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SOME EMOTIONAL ASPECTS OF THE TREATMENT OF DIABETES MELLITUS AND THE ROLE OF THE PHYSICIAN*

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DURING the past decade it has become increasingly evident that although the over-all incidence of degenerative vascular disease increases with the duration of diabetes, patients under good control show significantly fewer complications than those who have been poorly controlled.[1-4] Fully 70 per cent of the members of the American Diabetes Association subscribe to the concept of normoglycemia as a major objective of treatment, and another 23 per cent to the goal of aglycosuria.[5]

These objectives are not achieved in the majority of patients. Although statistics are difficult to obtain, reports from two large clinics indicate that only 13.5 per cent[2] to 22.4 per cent[6] of their patients have been well controlled as measured by strict normoglycemic standards. These results are probably representative of the general experience.

Failure to maintain normoglycemia in diabetic patients, however, can rarely be attributed to the disease itself. In most cases lack of success is ascribed to inadequate co-operation by the patients. It is common knowledge that the majority of patients do not satisfactorily follow their prescribed regimen.

Nevertheless, present efforts to lessen the high incidence of degenerative complications in diabetic patients are limited largely to diagnostic surveys and educational campaigns for the purpose of case finding and early treatment. Unfortunately, little consideration is given to the need for recognizing and investigating the reasons for failure to initiate or to maintain good control once the diagnosis has been made.

Undoubtedly, many of the difficulties in control arise from basic character and personality traits of the patient. Often, however, the precipitating factor is some action or attitude of the physician based on his lack of awareness of the real meaning of the patient's behavior, or his lack of skill in handling some of the issues that arise in the course of treatment. Accordingly, many treatment failures may justifiably be considered the fault of the physician.

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If, therefore, the results of treatment of diabetes are to be improved, attention must be focused not only on the early diagnosis and education of the patient but also on his treatment difficulties and on the technics by which they can most successfully be overcome. Some of these difficulties are similar to those involved in other medical therapies; others arise from the peculiar characteristics of diabetes.

DIABETES MELLITUS AS A UNIQUE PROBLEM IN TREATMENT

Unlike many chronic illnesses, the initial ten or fifteen years of diabetes are often asymptomatic even with poor or inadequate treatment. Since relief of discomfort is not at stake, and since normal activity is usually possible, many diabetic patients, and perhaps their physicians as well, lack two important incentives to the maintenance of good control.

Furthermore, the requirements for good control are onerous. Of the many conditions that must be treated by diet, few require the lifelong qualitative restriction necessary in many cases of diabetes, and none the total restriction of foods with high gratification value, such as candy, pastry, ice cream and other sweet desserts. Although other conditions occasionally need parenteral injections, none demand the daily self-administration of hypodermic medication whose omission might lead to disaster within a few days. Similarly, no other chronic illness requires the patient to confront himself each day (by urine testing) with the threatening results of any major deviation from meticulous self-treatment. Moreover, in the sense that the success or failure of treatment depends on the positive participation of the patient, diabetes differs from conditions in which alleviation or cure may be possible even when the patient remains completely passive.

To these unique and difficult aspects of diabetes may be added the following troublesome factors: the familial incidence of the disease, the tendency for diabetes to have peaks of onset at the emotionally critical prepubertal, pubertal and involutional periods, and the numerous incapacitating complications that are often neither cured nor prevented by average care.

Patient's Initial Reaction to the Diagnosis

Many future difficulties begin during the initial visits when the patient is told that the diagnosis of diabetes has been made. The diagnosis means different things to different patients. Only a few approach the problem realistically. To others the illness is merely "a little sugar" or "a touch of diabetes." This attitude either derives from similar points of view in diabetic friends or relatives or arises as a defense against having to deal consciously with all the implications of the diagnosis. Until it becomes certain why a patient is seemingly indifferent to the serious nature of his disease, the physician is wise to proceed cautiously with any attempt to break down this indifference. The patient who already indicates great apprehension by denying the importance of his illness is not served by being stripped of his defense.

Contrariwise, many patients are alarmed out of all proportion to the reality of the situation. They regard even the mildest diabetes as an overwhelming catastrophe, become alarmed about difficulties in arranging diets and frequently indicate their dread of future complications. Some of these patients have pre-existing anxiety states or identify themselves closely with diabetic friends or relatives who have suffered complications. Others utilize diabetes to make themselves invalids for the purpose of gaining attention or care or to serve their masochistic needs. Here, too, insight into the factors that lead patients to exaggerate the situation will enable the physician to understand how to reassure some and why it is not possible to reassure others by the usual means.

Technics of Reassurance

The attempt to reassure the patient is usually made when he is informed of his diabetes. Many physicians tell the patient that he can lead a normal life and take a normal diet (with certain restrictions and qualifications), that progress in the treatment of diabetes has extended the life expectancy almost to normal, and that strict adherence to the principles of good treatment will enable him to escape complications. This formula is factual and reassuring and saves time for the physician.

For some patients, however, mention of complications and reduced longevity at a time when the shock of learning of their diabetes has not yet been worked through may only increase the anxiety and fix attention on negative aspects of the situation. Moreover, an attempt at complete and final reassurance at this time is premature, since neither the patient nor his specific anxieties are adequately known at the first interview. Such gratuitous reassurance is often prompted by the physician's reaction to his own discomfort in having to give a patient bad news; a similar motive often causes the physician to minimize the importance of the diagnosis more than is realistically justified.

It is usually more effective to limit initial reassurance to emphasizing the positive aspects of the situation, to conveying the physician's own confidence and certainty, and to giving simple, honest, direct answers in the least disturbing manner to the questions that the patient asks. Subsequently, one may deal with the anxieties that arise from the patient's personality, his previous family experience with diabetes and the life setting in which the condition appeared. Specific management may be necessary when one is dealing with patient reactions that occur when diabetes develops at puberty or during the involutional period, in a young person before marriage or when childbearing is contemplated, in a person whose relative or friend has suffered an amputation or died in coma and in others going through any distressing experience.

Modifications of Approach Based on Patient Personality

The principle of individualization of treatment is applicable not only to the technics of reassurance but also to many aspects of the treatment of diabetic patients. Because the patient is personally responsible for carrying out the numerous details of his own treatment, the physician must solicit his cooperation in the most careful and skillful way. Alienation of the patient's good will often means that he will reject not only the physician but also what the physician asks of him.

It is of the utmost importance, therefore, for the physician to approach the patient with an adequate understanding of his personality. An important consideration is the degree of dependency that the patient is able to tolerate. It is best to allow patients who seem to be independent, intelligent and self-reliant to maintain their role and to permit them to consider themselves active co-participants in the management of their diabetes. At the other extreme are the excessively dependent patients to whom each detail of treatment must be carefully explained and for whom as much of the treatment as possible must be carried out by the physician, dietitian, clinic or visiting nurse. In addition there are many intermediate types of patients, of whom the most difficult is unwilling to be, or incapable of being, successful in carrying out his own treatment but who resents efforts that appear to place him in a dependent role.

The general approach to patients, the manner of teaching, the type of reassurance and the attitude of the physician and ancillary personnel must be based on a recognition of these variations in patient personality. Often, this is possible on an intuitive level, but when there is an apparent clash of personality between patient and physician, the physician should re-evaluate the situation in terms of whether

his approach to the patient may not be the provocative factor that interferes with effective treatment.

General Areas of Physician-Patient Difficulty

Interpersonal difficulties involving the patient and physician only rarely make themselves manifest. Most commonly they are expressed in ways that usually cause the patients to be designated as "uncooperative" or difficult." Such behavior difficulties are reflected in unnecessarily and frequently broken appointments, repeated tardiness in keeping appointments, unreasonable demands, unjustified criticisms, failure to accept or to carry out prescribed treatment and various other forms of provocation. These difficulties are most often related to particular aspects of the treatment of diabetes — namely, the self-administration of insulin, the diet and the discussion of the unfavorable treatment results shown by weight, blood and urine tests. It is precisely in these general areas that the physician is most likely to have to subject patients to emotional discomfort, and it is of obvious importance that he be alert to the real meaning of the ambivalent reactions that may result.

Problems Involved in the Diabetic Diet

Physicians often encounter great difficulty in getting patients to adhere strictly to the rigid dietary treatment of any medical condition, owing partly to reluctance to give up the pleasure of eating certain foods and partly to the rebelliousness of the average person against limitation of his freedom. In the juvenile diabetic patient revolt against diet may also be part of the adolescent effort to gain independence from parental domination. Among adult patients inability to follow a diet perseveringly is closely related to the factors that have already produced obesity in 80 per cent of these patients before the onset of the diabetes. A person's inability to limit his food so as to balance his energy requirements or, in more obvious cases, the gross overeating that results from tension in life situations usually has deep emotional origins. The physician must therefore understand that the average diabetic patient whose diet is to be curtailed cannot be approached only on the basis of personal appearance and health, but must also be treated on the basis of what is practical, realistic and emotionally feasible.

This approach necessitates reorientation of the physician in several ways. The practice of prescribing one of several stock dietary formulas invites patient failure in maintaining the diet, since no consideration has been given to the patient's cultural and national food habits or to his needs as an individual. Similarly, the dictum that underweight patients must be fattened and overweight patients must be reduced, although theoretically valid, is unsound in many cases. Neither the weight of the anorexic, mildly depressed patient nor that of the person with life-long compulsive overeating will respond merely to the prescribing of a theoretically proper diet.

Generally, patients who have gradually become slightly or moderately overweight as they have grown older and more sedentary are easiest to reduce by diet. The greatest difficulties are encountered in patients in whom obesity has existed since early in life and in those who have rapidly become excessively obese after some event of emotional significance, such as marriage, childbearing, menopause, an operation, death of a spouse or loss of financial or social status. In these cases it is usually wise to approach the matter of weight reduction gradually, without rigid insistence on prompt drastic weight loss, and even with provision for a periodic dietary deviation. In a few cases it is realistic to recognize the impossibility of weight reduction and to sacrifice this objective to make it comfortable for the patient to continue to co-operate in other important aspects of treatment.

Resistance to the Use of Insulin

The prescription of insulin to the diabetic patient also involves certain reactions that should be carefully appraised. It is a matter of simple observation that the injection of insulin is sometimes associated with a degree of anxiety, revulsion or fear that cannot be explained by the slight amount of pain involved. A few patients are never able to make their own injection, which must then be given by a nurse, parent or child. In rare cases fear of the injection completely precludes the administration of insulin.

These excessive reactions of a minority of patients occur in a rationalized form in many more who balk at taking insulin on the grounds of the possibility of life-long dependency, likelihood of insulin reactions, excessive pain, the danger of piercing of a superficial blood vessel or the production of local cutaneous nodules. Simple reassurance directed at the apparent cause of apprehension does not usually allay the patient's feeling of anxiety and tension when he is about to make an injection. Occasionally, such patients shortly after an injection complain of faintness or weakness, which may be mistaken for a hypoglycemic reaction if the physician is not aware of the emotional aspects of the situation.

Recognition that apparently trivial and unfounded complaints about insulin injections may be based on deeply rooted anxiety for which the patient finds superficial rationalizations enables the physician to be more realistic and tolerant, and more successful in dealing with the problem.

Management of Follow-up Visits

All patients normally have some degree of anxiety about illness. In diabetes, as in other chronic illnesses, the anxiety may have the life-long duration of the disease itself. Anxiety is most clearly ob-

served, however, at the onset of the diabetes or during subsequent complications, manifesting itself at other times in somewhat disguised and usually unrecognized ways.

Reactions of indifference, obsessiveness, passive resistance to and lapses from treatment, hostility to the physician and rebelliousness over diet are inimical to good results and are fully as important to the treatment of diabetes as any of the metabolic considerations. Moreover, the manner in which such reactions are approached by the physician is one of the major determinants of the success or failure of treatment.

The results of treatment must also be discussed at each visit. Because of the nature of diabetes mellitus and the requirements of treatment, the majority of patients fail to maintain treatment at a constantly optimal level. These errors and shortcomings must be elicited and dealt with in such a way as to enable the patient to accept the advice given. It is precisely in this area that many physician failures occur. As a result of such failures, negative patient attitudes are perpetuated, eventually resulting in chronic poor control.

A wide variety of poor technics of dealing with patient attitudes and poor treatment results may be observed in any diabetic clinic, and should be mentioned briefly. The exhortatory and inspirational technics have value for a limited time only, diminishing in effectiveness with each re-employment. Derogatory comparisons of the patient's behavior with that of ideal (and usually mythical) patients serve only to arouse resentment and really offer nothing constructive. Direct confrontation of the patient with discrepancies in his statements about weight, diet and urine tests (in essence, calling him a liar) serves even more distinctly to widen the gap between patient and physician. Angry and resentful reactions by the physician to the patient's failures merely convey the impression that the physician feels his authority or ability to have been slighted, and further convince the patient of his doctor's unfriendliness.

Perhaps the technic that causes most anxiety is the physician's more or less subtle implication that failure to comply with the minute details of treatment at all times will inevitably lead to disaster. Depending on the patient's knowledge and personal background, this conjures up visions of blindness, amputation, coma, insulin shock and hardening of the arteries; it frightens him but does not help him learn how to cope with the difficulties of treatment.

Patients deal with the anxiety produced by these physician attitudes in a manner characteristic of their individual personalities. Some simply escape by lapsing from treatment and returning only when a complication develops. Others operate on the principle of denial, acting as if their diabetes did not exist or as if it were a matter of no importance, but rarely admitting to any irregularity of treatment. Other patients become hostile and find fault with the physician, the diet, the inexperience or inefficiency of the dietitian, the inconsiderateness of the clinic secretary, the waiting time in the office or in the clinic and the failure of personnel to be sufficiently solicitous.

It is particularly apparent that most of the reactions of juvenile diabetic patients to discipline, authoritativeness or criticism by the physician are really identical with their reactions to similar situations involving their parents.

However provocative a patient may become, the physician must try to remain kind and understanding. Even the occasional display of an untherapeutic attitude by the physician is enough to interfere with the development of a relation that will enable him to obtain maximal co-operation from the patient. If the physician cultivates awareness of his own reactions to a difficult patient, he will be less easily drawn into retaliation or other negative behavior.

Physician-Patient Relation in the Treatment of Diabetes

Many features of the physician's attitude that contribute to the more effective treatment of diabetes have already been discussed. It should not be supposed that this attitude is merely a permissive one, although it might be in part described as "accepting." Nor should it be supposed that the abandonment of overcritical, threatening and punishing attitudes means giving up the primary objective of normoglycemia. On the contrary, the avoidance of such harmful attitudes, with emphasis on the development of a positive interpersonal relation, may be the most effective way to utilize present knowledge to attain the highest degree of physiologic control possible.

The psychologic objective of treatment should be the co-operation of the patient not through anxiety or fear of the disease or the physician, but rather through the wish to be well and to gain the physician's approval. To this end, the physician must be sympathetic and must understand the difficulties experienced by most diabetic patients in following treatment. He must recognize not only errors and defections but also achievements. He must be capable of providing the kind of encouragement that will help the diabetic patient in the daily self-denial required of him. He must be aware not only that the stresses and strains of life affect the patient's ability to persevere in treatment but also that important physiologic mechanisms contribute to poor control when set into operation by anger, fear, resentment, loneliness and dejection.[7, 8]

It is further required of the physician that he recognize realistically the fact that not all patients are capable of doing equally well and that all his efforts in some cases will produce no great success.

In the majority of patients, however, the results of the standard therapy of diabetes will be greatly improved if the physician adds to this therapy the orientation and attitudes described.

The fact that diabetes requires treatment for many years not only offers the physician a unique opportunity to fill an important supportive role in the patient's life but even demands that he do so.

Many of the points that have been discussed receive further illustration in the representative cases reported below.

Case Reports

Case 1. M. G., a 56-year-old cateress with a history of obesity, hypertension, multiple abdominal operations and many years of uncontrolled diabetes, frequently had severe insulin reactions and twice went into diabetic coma during 5 years of observation. The 2d episode of coma occurred during an acute exacerbation of her chronically disturbed relation with her ne'er-do-well husband. Subsequently, despite an increase of insulin to 92 units daily, she frequently had blood sugar levels over 300 mg. per 100 cc. and up to 10 per cent of sugar in the urine, often with ++ tests for acetone. Insistent efforts to induce her to stop overeating, which occurred several times a week during the pressure of preparing a large banquet or when difficulties with her husband and sons-in-law (whom she employed) became acute, led to increasing hostility on the patient's part, and she finally lapsed from treatment. Two years later it was learned that she had remained well on an unrestricted diet, taking 3 doses of regular insulin according to the urine tests before meals.

This patient needed and obtained relief from tension by excessive eating. Within a few years of her marriage, she had had to take over the support of the family and even after her catering business was well established still found it necessary to do most of the cooking herself and to employ a large number of dependent relatives. Her original choice of an occupation may have indicated her basic attitude toward food. Better control might have been effected if the physician had been less insistent on adherence to a diet and more aware of the total situation.

Case 5. S. B., a 37-year-old married, overweight woman, developed diabetes during a period of financial difficulty. She did well during the 1st year of treatment, but subsequently reverted to previous food habits and regained weight, the postprandial blood sugar rising to 207 mg. per 100 cc. Eighteen months after the beginning of treatment, her diabetic mother died of myocardial infarction. The patient then abandoned diet completely, was never sugar free, complained of polyuria, and had maximum postprandial blood sugar levels of 252 mg. per 100 cc., with 5 per cent sugar in her urine. Discussions of the situation by the physician were met with a consistent attitude of helplessness. No matter how she tried, it was never possible for her to follow a diet. Her husband was always bringing sweets into the house, her friends served chocolates and ice cream, there were sumptuous foods at various social functions that she had to attend, and it was impossible to refuse a rich luncheon when she went shopping in town or played cards with her friends. She amilingly enumerated her dietary indiscretions, shrugged her shoulders helplessly, and had no suggestion what to do about the problem. The patient's real panic became apparent only on two occasions, when she found a trace of reducing substance in the urine of her young nondiabetic son, whom she overfed.

This patient in various other ways covertly indicated her great anxiety about diabetes, which she associated very strongly with the death of her mother. Yet, after her mother's death, it became more difficult than before for her to follow a diet and control her diabetes. She could deal with this situation only by ignoring the reality of her illness and projecting the responsibility for her dietary indiscretions on others. To have broken down these defenses by sheer force would only have led to some other inadequate mechanism of dealing with the diabetes such as displacing her anxiety to some other area or abandoning treatment entirely. It was hoped that some treatment situation would eventually arise that would enable the physician to work through a better solution with the patient.

Case 7. F. L., a 46-year-old German refugee, had diabetes shortly after the death of her 2d husband. During the 1st few weeks, the disease was well controlled on a diet containing 160 gm. of carbohydrate, 90 gm. of protein and 80 gm. of fat. She regained 1 pound and had postprandial blood sugar levels of 145 and 172 mg. per 100 cc. She then read a diabetes manual and became greatly disturbed at the description of complications, particularly gangrene. Pain developed in her legs; she felt weak and became anxious about her health. Her anxiety was increased by the loss of 6 pounds, resulting from gross undereating in the course of the following month. The slightest degree of glycosuria terrified her. Long-suppressed memories of the death of her 1st husband, her children, her parents and siblings at the hands of the Nazis recurred. She talked a great deal about her own experience in a concentration camp with particular reference to starvation and the imminence of death.

This patient was given an opportunity to talk about these experiences and about the recent death of her second husband, was warmly and sympathetically reassured, and was encouraged to eat more adequately, with the suggestion that complications, for various reasons, were unlikely to occur in a patient like herself. She gained weight and remained in good control with postprandial blood sugar levels consistently under 200 mg. per 100 cc.

Case 8. M. S., a 47-year-old woman with a family history of diabetes, was found to be in mild acidosis in 1948. After hospitalization and control, she quickly abandoned all treatment except insulin, and successively consulted several physicians, whom she quickly found cause to abandon. In 1949 she consulted another physician, with whom she acted as with his predecessors — that is, she ate as though she were not diabetic, stopped making urine tests when she found them positive, postponed or broke appointments and disputed therapeutic suggestions. All attempts to help the patient deal realistically with her diabetes failed.

When the patient was hospitalized in 1952 for an orthopedic condition, efforts to control the diabetes were defeated by her difficult behavior. She complained repeatedly of errors on the part of the dietitian, of the quality of the food and of discrepancies between the trays and the diet sheets that accompanied them. When the physician asked her to save these diet sheets so that he could compare them with the prescribed diet, she repeatedly failed to do so. According to the dietitian, many of the patient's complaints were directed at diet substitutions that she herself had requested. The patient reproached her physician for not obtaining control of her diabetes even under these adverse conditions.

This patient's pattern of behavior consisted of repeatedly neglecting her diabetes to the point of making re-regulation necessary, but then defeating the attempt at treatment, often in such a way as to rationalize her rejection of a physician. It was believed that no satisfactory solution could be made of this situation but that neither this lack of success nor the patient's emotional difficulties required the

physician's discharging her from his care. Despite her behavior, the physician was still able to maintain a relation that enabled him to see the patient at least at irregular intervals and to be available to her for the management of acute or emergency problems.

CASE 9. F. L., a 55-year-old executive, was found to have diabetes at an insurance examination in 1937. On diet he reduced his weight from 205 to 170 pounds, at which level he was maintained. After the death of his physician in 1944 his previously excellent control deteriorated, the postprandial blood sugar levels occasionally rising as high as 276 mg. per 100 cc. Subsequently, however, he adjusted himself well to a second physician, insisted that he be seen monthly, and from 1947 to 1953 had 70 postprandial blood sugar tests, all of which were less than 182 mg. per 100 cc., except for 2 of 206 mg. during the course of colds. He assumed complete personal responsibility for the management of his prescribed diet and for changes in insulin dosage (20 units) when a cold or gastrointestinal upset necessitated such changes.

This patient's attitude toward his diabetes was that of complete realistic acceptance of a life problem for which there were certain obvious answers. He utilized his relation with the physician for the purpose of consultation exactly as he might consult with his attorney in the course of a business deal. His physician believed that he would be of greatest help if he accepted the role that the patient had given him.

CASE 10. M. C., a 62-year-old retired Italian bricklayer with diabetes of 16 years' duration, complained of poor control, frequent insulin reactions, weakness of the legs and blurred vision. He took 56 units of a protamine zinc and regular insulin mixture daily. He was not literate, and had never understood any of the diets that had been given him by physicians and various clinics.

Discussion disclosed his predilection for cheese, olive oil, green vegetables such as chicory and dandelion and a little wine each day. By permitting him to indicate what he would like for each meal, it was possible to draw up an adequate diabetic diet (containing 190 gm. of carbohydrate, 105 gm. of protein and 100 gm. of fat), which the patient believed to be of his own choosing. There were no subsequent major breaks in diet and minor deviations were completely ignored.

In the next 3 years the protamine zinc insulin dosage was gradually reduced from 56 units daily to 6 units on alternate days. The weight fell slightly, from 175 pounds to 168 pounds. Postprandial urine tests never showed more than blue-green reduction, and 14 post-prandial blood sugar tests ranged from 104 to 167 mg. per 100 cc. There were no insulin reactions. Vision improved, and weakness of the legs disappeared to the extent of permitting the patient to walk a distance of more than 3 miles from his home to the physician's office.

This case exemplifies the need for individual adjustment of treatment according to the patient's capacity to understand, his literacy and his national or cultural food habits.

CASE 13. E. S., a 70-year-old housewife, presented herself with a 4-week history of "acute" diabetes and a postprandial blood sugar level of 267 mg. per 100 cc. The patient and her husband had raised a large, successful family, but now lived alone. She was disturbed about having diabetes and at first displayed considerable anxiety not only about the idea that this was one more degeneration of old age but also about the possibility of losing a leg in the future. With diet she lost weight, and the blood sugar promptly fell to normoglycemic levels. In the next 4 years 16 of 17 postprandial blood sugar tests varied between 174 and 136 mg. per 100 cc. A single postprandial test during a respiratory infection was 231 mg. per 100 cc.

After the 1st few months of treatment, the patient concerned herself less and less with the possibility of diabetic complications and complained chiefly about symptoms associated with deprivation and loss of power — that is, her inability to eat freely, the stubborn constipation for which she constantly refused to follow any helpful regimen, and the difficulties of old age, such as the independence of her children and the lack of purpose in living.

It was possible for the physician to relate himself in a warm, filial way to this elderly woman, who showed clearly some of the emotional changes of aging, and to demonstrate interest in her complaints about lost functions (constipation and so forth). In the relation that developed, the patient remained well and co-operative in her efforts to please the physician and receive his commendation.

CASE 14. C. T., a 46-year-old garment worker, was referred by a diabetic aunt because of an 8-month history of weight loss and thirst. Examination disclosed glycosuria and a postprandial blood sugar of 286 mg. per 100 cc. The patient was a somewhat effeminate, small man who for years had devoted himself to calisthenics and steam baths for the purpose of maintaining his physical prowess. The development of diabetes was a considerable blow to his self esteem. During the 1st year of treatment postprandial blood sugar levels and urine tests were irregular partly because of a tendency to overeat foods containing natural sugar and to drink prune juice for the relief of constipation. Another source of difficulty was the patient's complete dependency on his wife, who from the beginning took over the management of his diabetes. Subsequently, however, on diet alone, the postprandial urine tests became consistently negative and over a period of 5 years, 14 postprandial blood sugar levels ranged from 100 to 192 mg. per 100 cc.; one test shortly after a Passover feast was 213 mg. per 100 cc.

The essential point in the treatment of this very dependent patient was to co-operate fully with his active wife in her management of his diabetes, at the same time avoiding injury to his façade of virile and aggressive masculinity.

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DIFFUSE GASTRIC POLYPOSIS*

Treatment by Total Gastrectomy

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SINCE diffuse gastric polyposis was first classified by Menetrier[1] in 1888, over 125 cases have been reported.[2-7] Other cases in the literature are described under the heading of "giant hypertrophic gastritis,"[8-12] which has been suggested as being synonymous with the second group of cases discussed by Menetrier — the rarer type, *polyadenome en nappe*. The case reported below belongs in this classification. Although it is a benign disease there are reports of associated cancer in 51 per cent of cases,[8] and the more recent reports therefore advocate total gastrectomy. All observers confirm the difficulty that both the radiologist and the gastroscopist have in ruling out a malignant lesion preoperatively. Several radiologists thought that the films in the case reported below represented either carcinoma or lymphoma, and the gastroscopist added hypertrophic gastritis, all three being the usual differential diagnoses encountered.

CASE REPORT

T. N., a 54-year-old man, was admitted to the hospital on October 18, 1948, because of thrombophlebitis of the right leg subsequent to an injury of the right thigh.

The past history revealed an appendectomy in 1920 and pneumonia in 1944. The patient was receiving disability compensation because of a "dropped stomach" present since World War I. For 30 years he had had occasional episodes of epigastric distress and "indigestion." He abstained from alcoholic beverages because they aggravated this distress. He denied vomiting, hematemesis and tarry stools. There were no previous gastrointestinal radiologic studies. The weight on admission was 140 pounds and had been in this range for many years. During World War I, he had weighed as much as 160 pounds on one occasion.

Physical examination revealed a thin, well developed man. He appeared anemic. The abdomen was soft, without tenderness or masses. Positive findings were limited to the right lower extremity, which showed moderate swelling of the calf without tenderness. Arterial pulsations were strong. Homans' sign was absent.

Examination of the blood disclosed a red-cell count of 3,000,000, with a hemoglobin of 8.1 gm. per 100 cc., and a white-cell count of 9400, with a normal differential. A test for occult blood in the feces was ++.

On the 2d hospital day, the right superficial femoral vein was divided and ligated. The immediate postoperative course was satisfactory. Therefore, studies were carried out on the 9th hospital day to explain the presence of anemia and occult blood in the stool. While these tests were being performed, the patient had an arterial occlusion affecting the right foot that was treated by right lumbar sympathectomy and anticoagulant therapy.

Gastric analysis revealed a fasting specimen with no free hydrochloric acid and a total acidity of 12 units. A second specimen taken 40 minutes after the administration of 0.5 cc. of histamine, showed 8.0 units of free hydrochloric acid and a total acidity of 22 units. An upper gastrointestinal series was reported as showing extensive submucosal infiltration of the stomach extending from the fundus to the antrum (Fig. 1). Lymphoma was the suggested diagnosis. Gastroscopy demonstrated a widespread infiltrating lesion of the stomach. The gastroscopist thought that this suggested lymphoma, carcinoma or benign giant hypertrophic gastritis. On November 30 a total gastrectomy, with jejunoesophagostomy and enteroenterostomy, was performed under fractional spinal anesthesia. Since the operator considered the gastric lesion to be malignant, he resected a 20-cm. segment of adjacent transverse colon; an end-to-end anastomosis was performed. Several days before discharge, the 1st, 2d and 5th toes of the right foot were amputated because of gangrene after the arterial occlusion.

FIGURE 1. *X-ray Film of the Stomach. Note the extent of the disease.*

After discharge on December 23, the patient progressed gradually to a well rounded diet. He was seen for follow-up study in March, 1953. At that time his weight was 130 pounds. He was eating 4 fair-sized meals a day and taking all types of food. The abdominal surgical incision was well healed, without herniation. The right foot was healed, although there was slight edema of the foot and ankle. Dorsalis-pedis pulsation was barely perceptible, and the posterior-tibial pulsation could not be felt. Popliteal and femoral pulsations were strong. Blood studies revealed a total protein of 5.8 gm. per 100 cc., with an albumin of 3.4 and a globulin of 2.4 gm., a hematocrit of 46 per cent, a hemoglobin of 13.0 gm. per 100 cc., a white-cell count of 10,000 and a prothrombin time of 14 seconds (control, 14 seconds).

Pathological examination disclosed a specimen consisting of an unopened stomach measuring 45 cm. along the greater curvature

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and 30 cm. along the lesser curvature (Fig. 2). The serosa was smooth and hyperemic. When the stomach was opened the entire mucosal pattern was seen to be abnormal except for the distal 6 cm. of prepyloric area. The abnormal mucosa was thrown up into huge folds, which were separated by crypts up to 4 cm. in depth. Multiple microscopical sections were studied.

FIGURE 2. *Photograph of the Gross Specimen.* *Note the similarity of the huge rugal folds to convolutions of the brain.*

There was a noticeable absence of any significant inflammatory-cell infiltrate in the mucosa, and none in the submucosa or muscularis. Some folds resembled true polyps (Fig. 3) having a stalk that contained muscle. In others the polypoid formations were for the most part composed of tufts of variously sized,

FIGURE 3. *Photomicrograph of the Stomach (X 2.5).* *Note in this field the formation of a true polyp with submucosa and muscularis up into the stalk. In addition there is hyperplasia of the mucosa, with many foci containing cystic glands filled with mucus.*

abnormally shaped glands without a true stalk (Fig. 4). In both types some glands appeared normal; others were large and cystic and filled with mucus. Although atypical, the epithelium did not appear anaplastic, no mitoses being seen, and there was no evidence of invasion.

DISCUSSION

This pathological finding was for the most part similar to that in the *polyadenome en nappe* of Menetrier. There was some disparity, revealing the difficulty encountered in previous reports of placing certain entities in specific categories. Figure 3 shows a definite polyp more closely resembling Menetrier's first category of *polyadenome polypeaux*, whereas Figure 4 demonstrates the more sessile type of epithelial hyperplasia. It is difficult to call this hypertrophic gastritis without significant inflammation, although Menetrier regarded both types as the result of inflammation. Whether it is a congenital anomaly is a moot point.

In 1926 Brunn and Pearl[4] collected 84 cases of diffuse gastric polyposis from the literature. Achlorhydria and bloody mucus on gastric lavage are suggestive of this disease. Of these 84 cases 12

FIGURE 4. *Photomicrograph of a Section of the Stomach (X 3.7).* *Note the hyperplasia and abnormal gland formation, without true polyp formation.*

per cent showed malignant degeneration. The authors collected 41 additional cases in 1943, the total incidence of malignant degeneration in polyps of either type being 51 per cent.

The symptoms of this entity are varied. They may point to a peptic ulcer or gastric cancer; other patients have only mild gastrointestinal abnormalities. Gastric hemorrhage may be the presenting symptom. In a review of 41 cases by Brunn and Pearl[4] 7 patients had hematemesis, and 14 others had gross or occult blood in the stools. Hypoproteinemia was a prominent feature in many cases.

A review of the literature[2, 3, 6, 8, 9, 11, 12] reveals 10 cases similar to that reported above, in 9 of which a total gastrectomy was performed. Patterson[12] advo-

cates removal of only the upper two thirds of the stomach, since this disease most frequently involves only this portion. The case described by Berne and Gibson[11] is interesting in that a similar change was discovered in the bladder mucosa at autopsy. The 3 cases reported by Palumbo et al.[8] included 1 in which there was associated malignant degeneration of the gastric mucosa with metastases to the liver.

The case presented above illustrates the difficulty in diagnosis. The entity precludes definite diagnosis by clinical history, physical findings, radiologic studies and gastroscopic examination. We believe that diffuse gastric polyposis can only be recognized after pathological examination of the tissue. Inflammation and edema can cause similar hypertrophy of the mucosa to confuse the radiologist, gastroscopist and surgeon. Despite the relative rarity of this condition it has already acquired more than one name, perhaps because of its varied picture as typified in this case. The incidence of thrombophlebitis appears to be quite high in the disease. Malignant degeneration reportedly varies from 19 to 51 per cent.

Summary

A case of benign diffuse gastric polyposis, treated by total gastrectomy, is presented. Ten similar cases reported in the literature are reviewed.

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THE CLINICAL TOXICITY OF TERRAMYCIN*

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FOR four months during 1951 and 1952, 5 gm. of Terramycin was given by mouth daily to a group of 70 tuberculous patients at Fitzsimons Army Hospital. Terramycin was used in combination with 2 gm. of streptomycin every third day primarily to study its effect on the rate of emergence of tubercle bacilli resistant to streptomycin. Streptomycin and Terramycin resistance did not occur in any patient receiving the full dosage schedule during or after the treatment period of one hundred and twenty days.[1] With the increasing use of Terramycin in the antimicrobial field, it was believed that a brief review of the clinical toxicity in the group studied would be of value, particularly since our experience differed from many of the published reports on Terramycin toxicity.

Review of Literature

Finland and his associates[2, 3] and Hendricks et al.,[4] in separate papers, described the occurrence of stomatitis or pharyngeal ulceration, or both, in patients receiving Terramycin. King[5] reported a mild, transient erythema. Finland and his coworkers[2, 3] observed a scarlatiniform rash, and Schoenbach, Bryer and Long[6] a maculopapular rash.

Blake, Friou and Wagner,[7] using varying doses of Terramycin (2 to 3 gm. a day) over periods ranging from two to thirty-six days, reported nausea, vomiting and frequent, loose stools in a study of 15 cases. Nausea occurred in 8, vomiting in 5, and loose stools in 9 cases. Nausea and vomiting, however, were described as troublesome in only 2.

Caldwell et al.,[8] reporting 168 cases of various infections treated with Terramycin, recorded the incidence of nausea alone as 10 per cent, nausea and vomiting as 10 per cent, loose stools or diarrhea as 13 per cent and substernal or epigastric pain as 2 per cent. All but 3 of these patients received 3 gm. of Terramycin a day. Three patients were given 6 gm. of Terramycin daily, and all 3 experienced nausea, vomiting and loose stools; 1 of the 3 also complained of vertigo. Seven patients had nausea and vomiting severe enough to require discontinuance of therapy.

McKenzie and Nugent[9] presented a series of 41 cases of urinary-tract infections treated with Terramycin in which no serious reactions occurred. The patients received approximately 1 gm. of Terramycin a day for three or four days. Most of the

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patients noted that their stools became somewhat softer. Diarrhea occurred in 1 case, in which it was distressing enough to require that the drug be discontinued.

In 93 patients with various infections who received the drug in the form of capsules, Timpanelli and his associates[10] noted only reactions consisting of gastrointestinal disturbance. Fifty-four per cent had no reactions; 25 per cent had mild symptoms, 11 per cent had moderate symptoms, consisting of several diarrheal stools daily and vomiting once or twice in the course of treatment, and 10 per cent had persistent vomiting and diarrhea, usually necessitating discontinuance of the drug. Mention was made of 67 additional patients who received Terramycin in the form of compressed tablets. It was believed that toxic manifestations were about twice as high in this group.

Loughlin and Joseph[11] reported only nausea, vomiting and anorexia in 5 children treated for yaws. All were less than eight years of age, and toxicity occurred when approximately 8 to 10 gm. of Terramycin had been given (on the fourth to the fifth day of therapy).

Nesbit et al.[12] described 24 patients who received 4 to 6 gm. a day for varying periods. There was no apparent alteration of the blood count and no retention of bromsulfalein. Anorexia and mild nausea were not uncommon, but actual vomiting was rare and was confined to women. A dermatitis venenata occurred in 1 patient, who had experienced the reaction with other chemotherapeutic and antibiotic agents.

Potterfield and Starkweather[13] gave Terramycin in a dose of 30 mg. per kilogram of body weight to 62 children for an undisclosed length of time. No toxic manifestations were observed except for the occurrence of dark-green, soft, mushy stools in some cases.

Wright and his associates,[14] reporting 100 surgical cases in which Terramycin was used in a dose of 1 or 2 gm. for two to fourteen days, observed no nausea, vomiting or diarrhea.

In a study of 91 patients with pneumonia, Jackson et al.[15] described, in addition to frequent and severe gastrointestinal symptoms, replacement of the sputum and fecal flora by staphylococci in many cases. Infections, both pulmonary and intestinal, resulted in some cases from these floral changes and were believed to be the contributing cause of death in 5 cases.

De Mangus[16] reports what he considered to be a nearly fatal reaction to Terramycin characterized by generalized edema, dyspnea, albuminuria, cylindruria and numerous red and white cells in the urinary sediment.

A crossed, fixed drug eruption was described by Welsh[17] in which Terramycin caused a skin reaction identical to one that had previously been produced by Aureomycin.

Geraci[18] listed anorexia, nausea, vomiting and diarrhea as the only toxic manifestation to Terramycin in 6 of 9 patients with subacute bacterial endocarditis receiving 3 gm. daily for one to three weeks.

Previous Study

Previously, at this hospital, 15 patients were given Terramycin in a dosage of 7 gm. a day for one hundred and twenty days, and 12 patients received 7 gm. every third day for one hundred and twenty days.[19] In these patients audiometric and caloric tests were done at the beginning and end of therapy. No evidence of ototoxicity was observed. Urinalyses and renal-function studies as measured by phenolsulfonephthalein excretion and blood urea nitrogen failed to give any evidence of nephrotoxicity. Since there was no alteration of bromsulfalein retention, cephalin flocculation or prothrombin time, the possibility of hepatotoxicity was also excluded. No patient manifested glossitis, pruritus or dermatitis. Hematologic studies did not reflect any abnormalities except the changes found in active pulmonary tuberculosis.

Present Study

In the present series of 70 patients, as in the first group of 27, no ototoxic, nephrotoxic, hepatotoxic, avitaminotic, dermatologic or hematologic changes were noted. The signs and symptoms of gastrointestinal-tract irritability were the only clinical manifestations of Terramycin toxicity observed. Anorexia was the most common symptom, occurring in 70 per cent of the patients. It usually began on the first day and, as a general rule, persisted throughout the four-month period of treatment.

Nausea, the second most common symptom, occurred at least once in 50 per cent of the patients. In the individual case nausea was sporadic and transient as a rule. There were 4 patients, however, in whom this unpleasant side effect was more or less persistent.

Vomiting was observed at least once in 9 (12.8 per cent) of the 70 patients studied. In 4 cases it persisted when 5 gm. was taken. All 4 patients, 2 of whom were women, were able to continue Terramycin by either intermitting or reducing the dosage. The vomiting and the accompanying nausea did not constitute a serious problem, being alleviated, in the majority of cases, by administration of Terramycin with meals. Frequently, 30 to 60 cc. of cream or corn syrup, or both, solved the problem in the less serious cases. The addition of such measures as atropine administration, mild sedation with phenobarbital and the use of Dramamine proved effective in the more serious cases.

The fourth manifestation of Terramycin toxicity observed was the occurrence in the individual patient of one to four soft stools per day. This was observed in 70 per cent of the cases and usually persisted

during therapy. (This can hardly be regarded as a toxic manifestation since it was not troublesome or annoying to the patient; nevertheless, it was a change that must be attributed to Terramycin.)

Lastly, a mild diarrhea was observed occasionally by a few of the patients who experienced the frequent soft stools. This was a rare finding, always transient, and was never difficult to control when such measures as bismuth and paregoric or a kaolin and pectin mixture were employed.

The patients with the most toxic reactions — those experiencing nausea, vomiting and diarrhea — were carefully examined by proctosigmoidoscopy; no deviations from the normal were found.

Discussion

These side effects of Terramycin can probably be interpreted in terms of the common denominator of weight loss. When weight gain or loss in excess of 5 pounds is regarded as significant, 16 (22.9 per cent) had weight loss, 22 (31.4 per cent) had no change, and 32 (45.7 per cent) had weight gain. Another measure of these side effects can be realized from the fact that 4, or 5.7 per cent, of the 70 patients could not tolerate the full dosage schedule of Terramycin.

It is of interest that 2 patients had an active duodenal ulcer, and 2 had an inactive duodenal ulcer at the start of therapy. The former healed during the one hundred and twenty days of Terramycin, and the latter showed no reactivation.

Summary and Conclusions

Observations on the clinical toxicity of Terramycin were made on 70 tuberculous patients receiving 5 gm. of the drug daily in combination with 2 gm. of streptomycin every third day, both drugs being given for one hundred and twenty days.

Five grams of Terramycin administered orally for one hundred and twenty days represents a larger quantity of the drug and a longer period of therapy than most clinicians throughout the country have had experience with to date.

Gastrointestinal-tract irritability, with resulting anorexia, nausea and vomiting, was the only toxic manifestation to Terramycin that was observed in the study.

Contrary to many reports in the literature, this series indicated that the gastrointestinal-tract irritation due to Terramycin is not a serious problem since no patient had to have the drug discontinued during the four months of administration, and only 4 (5.7 per cent) had to have the dosage reduced.

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A CHRONOLOGIC ACCOUNT OF THE MEETING PLACES OF THE MASSACHUSETTS MEDICAL SOCIETY AND ITS COUNCIL

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THE meetings of the Massachusetts Medical Society were held in many places for a hundred and seventy years before the present building was acquired as a permanent headquarters. The following chronologic account is an attempt to record the story of these meeting places since the Society was incorporated. Many of the sites have historical interest.

During the early years the Society occupied in harmony the same quarters as the American Academy of Arts and Sciences. As time went on, however, sporadic attempts were made to obtain a more permanent home. These efforts always failed from lack either of funds or of co-operation between the Society and other organizations or institutions.

The first meeting was held in Old County Court House on Queen Street, later Court Street, on November 28, 1781. The second meeting took place on April 17, 1782, and the first real annual meeting on June 5, 1782.

The Council, consisting of seven members, held its first meeting on July 18, 1782, both the Society and its Council meeting in the Old County Court House until the fall of 1783, when both met in the "Manufactory House," a building covering the land at the northerly corner of Tremont Street and Hamilton Place now occupied by the Phillips Building. The original building belonged to the Commonwealth of Massachusetts and was used as a barracks during the Revolution.

The American Academy of Arts and Sciences held three meetings in the Manufactory House — one in 1783 and two in 1784. The Massachusetts Medical Society approved of gathering at this place, and a committee was appointed to confer with a committee of the Academy to make the necessary arrangements. The Society met there twice in October, 1783, as well as in April, 1784, and June, 1784. The Massachusetts Bank occupied the Manufactory House in the spring of 1784, and on November 15, 1784, it was "Agreed that the medical society be allowed to meet in the stockholders chamber four times in the year provided it does not interfere with any business of the Bank." In July, 1784, the Society had returned to the County Court House; in May, 1785, the meeting was in the Senate Chamber of the Old State House, and in June at the County Court House again.

For some unknown reason, the Society again returned to the County Court House. At the first meeting in "Mr. Furnass's painting room in Court Street" on October 26, 1785, eleven fellows were present (during the next year it was called "their hired room in Court Street"). Although an order of the General Court dated March 24, 1786, permitted the Society and the Academy to hold meetings "in some one of the chambers or lobbies of the State House [Old State House] until further order," the Society still met in the painting room in 1787, 1788 and 1789.

The Council met in the Old State House at times and wherever it was convenient at other times, the place of the meeting not always being stated in the minutes. It met in Cambridge in May, 1786, having used the Senate Chamber the previous March, in the Selectmen's Room in March, 1788, and again in October of that year and in the Senate Chamber again in May, July and October, 1789. It met at Vila's tavern or hotel, as it was called, or in the room of the American Academy of Arts and Sciences, after reorganization, until 1810.

The records do not say where meetings were held from 1816 to 1822, when the Council met "at the Medical College, Boston." In 1841 the May meeting was held in Masonic Temple.

In 1853 the Council and library† moved to a room in Phillips Place, opposite King's Chapel. No further change in meeting place was made until February, 1856, when the first meeting was held in a new room in Perkins Building, 12 Temple Place. The records of the Council state that it held two meetings in 1869 in "Avon Street." (The meetings were at the usual place, 12 Temple Place, but from March 30 to June 9 of that year the place was called Avon Street, the name "Temple Place" being restored on June 9.)

The Council moved its headquarters to 36 Temple Place, formerly the residence of Thomas Handasyd Perkins, on February 2, 1870, the building being occupied in that year by the Provident Institution for Savings. The Council remained there for nine years. The Council, with the Society, had headquarters with the Boston Medical Library at 19 Boylston Place after 1879, until its first meeting on February 6, 1901, in the new library building at 8 Fenway.

In October, 1790, the Society began to hold its meetings in Concert Hall, a brick structure dating from Colonial times, on the southerly corner of Hanover and Court streets, where it continued to meet until the reorganization in 1802-1803. Before the Revolution the building was a resort of the

*Formerly, president, Massachusetts Medical Society; chairman, Committee on Headquarters during purchase and remodeling of 22 Fenway.

†The library of the Society, begun in 1782, was kept in the home of the librarian. It was disposed of ninety years later to the Boston Public Library.

Friends of Liberty, and American prisoners captured at Bunker Hill are said to have been tried there by a military court. Concert Hall was a tavern in 1792, kept by James Vila (the minutes of the meeting on October 6, 1802, state "held by adjournment at James Vila's"). The building, which was torn down in 1869, was presided over for forty years by the restaurateur, Peter Bent Brigham, who left his fortune to found a hospital in Boston. During this early period, regular meetings were held at least three times a year, with many Council meetings in addition.

Dr. J. D. Treadwell, of Salem, was responsible for the Reorganization Act, which was passed on March 8, 1803. The first meeting after reorganization was on April 28, and the first stated meeting on June 1 of that year. The annual meeting of 1804 was held on June 6 in the "Library Room" or "Franklin Hall" in Franklin Place, the subsequent gatherings being held there until 1810, when rooms in White's building at 49 Marlborough Street (Washington Street), the building to which the Harvard Medical School had moved, were occupied. In 1814 an attempt was made to co-operate with Harvard in the erection of the Mason Street building for joint use by the Medical School and the Society.

On February 7, 1816, the Council appointed a committee to obtain a lease of a suitable place for holding the meetings of the Society, Council and censors, and to house the library and records. The minutes of the next meeting state that the library had recently been moved, suggesting that a move had been made to the building of the Massachusetts Medical College in Mason Street, although the records of neither Council nor Society indicate where meetings were held for the next eight years. The Council records for October 2, 1822, state that a session was held "at the Medical College, Boston," and the next meeting of the Society, in 1823, was "holden at the hall of the M. M. College, Boston." Agitation for new quarters began in 1825.

A scheme to join with the American Academy of Arts and Sciences in the construction of a building on land belonging to the Athenaeum did not materialize. The Athenaeum built the building without outside assistance on Pearl Street near the corner of High Street, and on February 22, 1827, granted a lease to the Massachusetts Medical Society of "the North East Room in the basement story of the new building belonging to the Athenaeum," with sufficient space for the library and other property of the Society, for an annual rental of $125. The first meeting of the Society in the new quarters was held on Wednesday, June 8, 1827.

The question of erecting a building for the Society was revived in 1833, and in October, 1834, a committee appointed to consider the expediency of obtaining more permanent quarters reported that the funds of the Society were not sufficient. A committee for the same purpose was appointed in May, 1838, and in the following year Dr. Peirson broached the project of a joint stock company, in which the permanent fund should be invested.

The annual meeting was held in the Masonic Temple, at the corner of Tremont Street and Temple Place, in 1839 and 1840 and in 1841, when a definite arrangement was made for rooms in that building; the Council met there in May, the Society convening in the large hall. The headquarters remained there until 1853, when the Society met in the hall of the Lowell Institute, at the rear of 233 Washington Street, and the Council and library moved to a room in Phillips Place.

On May 28, 1851, the Society met in the City Hall, Worcester, the Council having held a meeting in Worcester on the previous day. Subsequent meetings outside Boston — in Pittsfield (1852), Fitchburg (1854), Springfield (1855), New Bedford (1857) and Pittsfield (1863) — were not considered so successful as the meetings held in Boston.

On its seventy-fifth anniversary (May, 1856) the Society met in the hall of the Lowell Institute in Boston, with over 500 members participating. No annual dinners were held in 1861, 1862 and 1865. The annual meetings of 1862 and 1864 were held in the "Common Council Chamber" of the Massachusetts Charitable Mechanics Association at the corner of Bedford and Chauncy streets in Boston. The question of a two-day session of the annual meeting was first proposed at the annual meeting of the Council on May 24, 1864, a favorable report being accepted at the meeting of the Council in February, 1865. The first two-day meeting was held in the Lowell Institute in 1866.

After a session in the hall of the Lowell Institute in 1866 the Society met again in the quarters of the Massachusetts Charitable Mechanics Association in 1867, and in the new operating theater of the Massachusetts General Hospital in 1868. Subsequent meetings were held in Bumstead Hall, under Music Hall, in Music Hall Place, off Winter Street (1869) and in Horticultural Hall, opposite the Granary Burying Ground, on Tremont Street, between Bromfield and Bosworth (1870). The Society returned to the hall of the Lowell Institute from 1871 to 1879. The meetings of 1880, 1881 and 1882 were again held in Horticultural Hall.

On June 7 and 8, 1881, the Society celebrated its centennial anniversary, the annual dinner being held in Music Hall, Winter Street. In 1883 the place of meeting was Huntington Hall, the new auditorium of the Rogers Building of the Massachusetts Institute of Technology on Boylston Street.

The headquarters of the Society and the Council was with the Boston Medical Library at 19 Boylston Place after 1879. From 1889 to 1901 meetings were again held in the hall of the Massachusetts Charitable Mechanics Association on Huntington Avenue, where there were sufficient accommodations for

section meetings, a commercial exhibit, the meeting of the Society and the annual dinner.

On February 7, 1900, the Council voted "That the Committee on Membership and Finance be requested to report to the council in June next what action should be taken by the Massachusetts Medical Society to secure rooms and accommodations for the meetings of the councilors, censors, sections, committees, the annual meeting (excepting the dinner) at an expense not exceeding one thousand dollars per annum." On June 12 of that year the Council voted as follows:

> That the treasurer of the society be instructed and is hereby authorized to conclude arrangements with the Boston Medical Library whereby, at an annual rental or expense not exceeding seven hundred and fifty dollars ($750) and for the term of three years beginning January 1, 1901, the Massachusetts Medical Society shall have in the new building of the said Library on the Fenway, in Boston, suitable and acceptable accommodations for all its councilors' meetings (stated, special, business and social); the meetings of its censors, acting as censors at large; all its committees; the sessions of its boards of trial; its archives and records; its Librarian's office and the storage of its publications and the meetings of its sections; the arrangement by lease or other equivalent instrument to include the lighting and heating as well as the use and occupancy of the several halls and rooms.

The Society moved into the new quarters on January 1, 1901, the exercises of the first day of the annual meeting in 1901 being held in the new building at 8 Fenway; the Society itself met in Chickering Hall on Huntington Avenue, and the annual dinner was held in Symphony Hall. The Boston Medical Library building remained the headquarters of the Society until the opening of the new building at 22 Fenway.

The first evening dinner (1912) was served in Mechanics Building, with 940 fellows and guests present. In 1921 a mid-day dinner held because of protests regarding the evening hour was not successful, and the custom of evening dinners was resumed. Before 1914 the dinner was free. In that year, a charge of $1.00 was made.

A movement, begun in 1913, to have the *Boston Medical and Surgical Journal* become the official organ of the Society, took effect in June, 1914, and the Society bought the *Journal* in 1920. The annual meeting of 1923 was held in Pittsfield.

The Boston *Directory* gives the official headquarters of the Society as 8 Fenway from 1901 through 1927; "8 Fenway and committee rooms at 126 Massachusetts Avenue" in 1928 and 1929; 8 Fenway and 165 Newbury Street in 1930 and 1931; and 8 Fenway from 1932 on. Mr. James F. Ballard, director of the Library, explains that space was not sufficient for business activities of the Society until the new wing was added; the *Journal* and all Society activities moved there after 1930.

In the Council Meeting of October 5, 1927, Dr. T. J. O'Brien, assistant to the President, pointed out that the committee room at 126 Massachusetts Avenue, Boston, had been outgrown as a headquarters for the Society. And at the meeting on February 1, 1928, Dr. E. A. Knowlton made the motion that "the chair appoint a committee of five to consider ways and means of acquiring a permanent home for the Massachusetts Medical Society." This motion was passed by the Council. The President, Dr. John M. Birnie, appointed the following five members: Dr. John M. Birnie, Dr. T. J. O'Brien, Dr. S. D. Woodward, Dr. Henry Colt and Dr. C. G. Mixter.

This committee immediately went to work, and by June of the same year had received a substantial number of contributions to the building fund, the first, in the amount of $500, being received from Mrs. Rose Paddock Crane in memory of her father, Dr. Franklin K. Paddock, of Pittsfield, a former president of the Society.

In June of the same year, the committee reported to the Council that it had decided to change the Society's drive for funds into a joint drive with the Boston Medical Library with the understanding that one sixth of the total income would be allotted to the Society. The list of donors to this original drive, in the handwriting of Dr. Arthur K. Stone, treasurer of the Society, is still in the Society's vaults.

At the meeting of the Council in October, 1929, the Committee on a Permanent Fund reported that it had acquired pledges of $172,259 in the joint drive and that about $18,000 had actually been paid in by the members. This drive continued through December 31, 1929, when the building fund was turned over to the Society in the amount of $19,195.94.

Additional subscriptions and interest from the fund itself brought the total to $47,000 in 1932 and $49,000 in 1933. The fund had grown to approximately $56,000 by 1936, and to over $60,000 in 1938. This fund continued to grow with moderate additions until 1949, when it stood at $76,072. It was at this time that the Council voted to peg the general funds at $250,000 and to give any excess income to the building fund, so that during 1949 and 1950 the fund increased rapidly until December 31, 1949, just before the purchase of 22 Fenway, when it stood at $121,398. To this another contribution was made from the excess of the general funds, so that on December 31, 1950, the total value of the building fund, including the building itself and improvements, stood at $309,000.

At the annual meeting in June, 1928, the Committee on a Permanent Home presented six different motions regarding the powers of their committee. The last of these was, "that in any temporary or permanent headquarters proper recognition be given to any memorial gifts." The only definite memorial gift of which there is a record was that of April 13, 1928, from Mrs. Rose Paddock Crane, referred to above. There is also mention of a memorial to Dr. Ayres T. Merrill, of Pittsfield, to which a number of physicians subscribed, mostly in small amounts.

According to the only records available the total amounted to $255. Dr. Samuel B. Woodward, a former president, contributed $500 in 1928, and Dr. Walter P. Bowers contributed $600 in the late 1930's. These two gifts, however, could hardly be considered as memorials. The records of the Council mention gifts in memory of Dr. James S. Stone, who was president from 1925-1927, but the amount of this memorial is not specified.

At a meeting of the Committee on Society Headquarters on October 16, 1952, the question came up about the pamphlet on Society Headquarters, and it was believed that the names of the persons who had made large contributions to the original headquarters fund should be included.

The following is a list of those who contributed over $100:

Rose Paddock Crane (in memory of her father, Franklin K. Paddock)	G. M. Albee Worcester
Hervey L. Smith Springfield	Benjamin F. Andrews Worcester
Irving R. Calkins Springfield	Ernest B. Emerson Rutland
E. A. Bates Springfield	Michael F. Fallon Worcester
Frederick B. Sweet Springfield	Arthur W. Marsh Worcester
E. L. Davis Springfield	F. H. Washburn Holden
Lincoln Davis Boston	Leonard Wheeler Worcester
Franklin S. Newell Boston	Edmund H. Stevens Cambridge
E. Stanley Abbott Boston	Charles O. Thompson Boston
W. L. Richardson Boston	Samuel B. Woodward Worcester
John L. Morse Boston	C. Morton Smith Boston
Lawrence C. Swan Beverly	H. D. Davidson Springfield
James S. Stone Boston	E. P. Joslin Boston
Alexander Quackenboss Boston	Walter P. Bowers Clinton
Peer P. Johnson Beverly	Frank R. Ober Boston
Charles G. Mixter Boston	Robert N. Nye Boston
	Memorial to Ayres P. Merrill Pittsfield

In 1942, when it became obvious that the Society needed more office space than could be provided by the Boston Medical Library, many efforts were made to purchase 22 Fenway, a building that had been designed by Mr. Robert Peabody, an architect, for his own home, and was then owned and occupied by a Greek-letter fraternity of Massachusetts Institute of Technology students.* All these efforts fell through until May, 1949, when the Council voted the sum of $5000 to be used under the direction of the Headquarters Committee to make a complete study of the needs of the Society, and to produce plans to meet its requirements.

On October 5, 1949, the Committee obtained the services of Mr. H. I. Beckwith, professor of architecture at Massachusetts Institute of Technology. Mr. Beckwith made a thorough study of the Society's needs and presented several plans to the Headquarters Committee, with the recommendation that 22 Fenway be purchased for the sum of $75,000. Mr. Beckwith was able to arrange for the purchase, and the property was bought on July 14, 1950.

On July 28 the Headquarters Committee met with the architect, who presented plans for reconstructing the building, including a fourth-floor addition, and furnished an estimate consisting of architectural and engineering costs of $158,603. The available money in the building fund then amounted to $63,000.

The whole Committee passed by unanimous vote the following recommendation to the Council: that an additional $100,000 be transferred from the General Fund to the Building Fund for the purpose of remodeling and furnishing the building. The Council on October 4, 1950, voted to accept the recommendation of the Headquarters Committee.

It was also voted that the General Fund be limited to $100,000 and that any surplus be credited to the Headquarters Maintenance Fund.

The final cost of 22 Fenway was as follows:

Purchase cost including lawyers' fees, proportionate taxes, etc.	$ 80,843.41
Total alterations, including elevator, built-in vault, construction of fourth floor, general reconstruction, plumbing, heating, etc.	170,685.30
Total office furnishings, portable equipment, together with all movable structures, such as the memorial plaque, pictures of past presidents, etc.	16,399.30
Grand Total	$267,928.01

The headquarters was ready for occupancy in the late spring of 1951. Two hundred and thirty-four groups used the building during the first year of occupancy, and there were over 31,000 incoming and outgoing telephone calls over the switchboard.

The Society may now rest secure for at least another twenty-five years, and if the growth of its internal workings increases, land that it owns is available for any needed further expansion.

*The house had been on the market in 1930, when the Committee inspected the premises. The asking price was then $70,000, but the committee was advised that it might be obtained for less. It was decided that the building was not adapted to the needs of the Society, and that the cost of extensive alterations and maintenance would be more of a burden than should be assumed in that year of depression.

MEDICAL PROGRESS

PRESENT-DAY CONCEPTS OF SHOCK (Concluded)*

HOWARD A. FRANK, M.D.†

BOSTON

Therapeutic Considerations

Blood replacement and surgery. Among the important advances in the management of wound-shock is the establishment of the principle that the surgical treatment of the wound is an integral feature of the therapy of shock.[22] Therefore, an immediate objective of blood-volume replacement is to bring the patient into condition for surgery, so as to terminate blood loss, control the spread of infection and permit recovery. This point of view led to a reorganization of medical facilities for the care of the severely wounded on the field, with the elimination of separate centers of "resuscitation."

The many studies of blood volume in injured soldiers and civilians have provided guides to transfusion therapy.[10, 16-22, 24, 25] If the arterial pressure is below 100 as a result of blood loss, a loss of at least 30 per cent of blood volume has occurred. A patient of average size, in a moderate degree of shock (with, for example, an arterial pressure of 80), has lost about 2 liters of blood. In more severe degrees of shock, blood-volume reductions of 60 to 75 per cent have been observed. Whole blood is to be given rapidly in an amount sufficient to replace the blood lost. In the absence of active sepsis, failure to respond may be taken as evidence of inadequate replacement or continuing blood loss. Beecher[10] discusses considerations of economy in blood administration, when large numbers of casualties drain the available supplies of blood and impose a delay in bringing the patient to surgery. A rise in arterial pressure to 80 to 100, an improvement in pulse quality and the return of skin color and warmth indicate sufficient restoration of circulation to prevent progressive deterioration during a waiting period. Protective bandaging and immobilization are required for reduction of pain, bacterial contamination and loss of plasma and blood into the wound. Additional blood loss during surgery may be extensive.

Urine formation at the rate of 1 cc. per minute is a reliable index of adequacy of peripheral blood flow. Catheterization of the bladder for continuous observation of the rate of urine formation has been particularly helpful as a guide to the complex fluid and electrolyte requirements imposed by severe burns.[23, 189] If dehydration is suspected as the cause of oliguria, a test infusion of a liter of 5 per cent glucose in water may be given and the effect upon the rate of urine flow observed. Resumption of flow is prompt if oliguria is due solely to dehydration. Replacement of blood volume and restoration of arterial pressure after a period of shock do not immediately release renal vasoconstriction. The persistence of oliguria or anuria should not be allowed to lead to excessive fluid therapy. If renal damage consequent to shock persists for days, as it may, fluid administration must be limited to the amount required to replace extrarenal losses once it is clear that the blood volume is normal.

In an extensive trial during World War II plasma was found very useful for restoring lesser degrees of blood-volume deficit and for sustaining life until whole blood could be given. But patients given plasma only for full replacement of a major blood loss were severely anemic and tolerated surgical procedures poorly.[17, 21, 22] Whole-blood transfusions given thereafter at times led to plethora, pulmonary congestion and pulmonary edema. The objections to plasma therapy are less in forms of injury that produce a predominant loss of plasma, but a considerable degree of red-cell loss also occurs frequently (especially in burns or sepsis) so that a progressive anemia develops. This may be anticipated to some degree by the use of whole blood instead of plasma. An elevated blood viscosity is not a significant handicap when blood volume is normal and the vascular tree is not narrowed.[58, 190] The space-occupying function of the erythrocyte is emphasized by Moore[191] in the therapy of extensive injuries producing a local increase in capillary permeability.

The chief advantage of plasma is the fact that it may be stored for long periods and is immediately available. Its chief disadvantage is the danger of transmission of viral hepatitis. A discussion of current efforts to increase the survival of red cells in storage, to sterilize plasma and to provide satisfactory substitutes for plasma is beyond the scope of this report.

Sedation and anesthesia. In an earlier period morphine was given as a specific for shock. Beecher's[10, 25] observations indicate that most men in moderate and severe degrees of shock do not require medication for relief of pain. When this is required, 10 mg. of morphine, given intravenously, is likely to be as effective as a larger dose. Apprehension is better treated by small doses of short-acting barbiturates given intravenously. Poisoning may result from multiple subcutaneous doses of morphine, which remain unabsorbed until blood flow is restored by

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transfusions. The safest anesthetic agent for severely injured men is ether, in the view of Beecher and his colleagues,[10, 25, 192] who warn against intravenous barbiturate anesthesia. British observers find less objection to barbiturate anesthesia and consider the manner of administration to be more significant than the choice of agent.[24] Experimental evidence supports the warnings against barbiturate anesthesia in shock. Spinal anesthesia is also dangerous and likely to provoke a drastic fall in arterial pressure. It is best avoided in the presence of severe injury or sepsis.

Pressor or antipressor therapy. The vasoconstrictor response is not maximal even in severe shock, for the arterial pressure can usually be raised for a time by pressor drugs. Is cardiac output or blood flow through critical vascular beds improved at the higher arterial pressure levels so produced? This question has not aroused much interest in connection with clinical wound shock, since it is clear that pressor therapy is not a substitute for blood replacement, may mask the fact of persisting blood volume deficiency and, by intensifying renal vasoconstriction, may delay renal recovery. However, there may be a place for pressor therapy in states of shock that are not primarily due to blood loss or in which blood replacement has failed. Recent clinical and experimental work has centered about norepinephrine and other amines, which have a vasoconstrictor effect and are relatively free of the undesirable effects of epinephrine on metabolism, pulse rate and central nervous system. Norepinephrine or paredrine did not increase cardiac output or prolong survival in experimental hemorrhagic shock.[174, 193] During the relatively brief period in which the arterial pressure was raised by norepinephrine, renal blood flow was reduced, hepatic blood flow was not changed, and adrenal, cerebral and coronary flows were increased.[174] Continuous infusions of nor-epinephrine in various states of vascular collapse in man have been observed to sustain arterial pressure for days, during which urine output is maintained. Blood-flow measurements are not given in these case reports.[194-198]

On the other hand, the usefulness even of the unaided vasoconstrictor response has been questioned by experimentalists who find that the preliminary administration of Dibenamine, an antiadrenergic drug,[199] increases the tolerance of dogs to hemorrhagic hypotension.[200-202] But in most of the experiments reported, it is clear that Dibenamine-treated dogs bleed less in arriving at a given level of hypotension. Untreated dogs can tolerate blood loss that is fatal for fully Dibenamine-treated animals. Furthermore, Dibenamine or more rapidly acting antiadrenergic drugs do not prolong survival when given after shock has been allowed to develop.[203] There is no doubt that vasodilatation is tolerated well when blood volume is normal and the position is horizontal or head-down,[204, 205] but there is little reason to believe that pharmacologically induced vasodilatation will be useful after a substantial reduction in blood volume has already occurred. Its usefulness in shock persisting in spite of transfusion therapy that has produced plethora remains to be evaluated.

Adrenocortical therapy. The sharp reduction in tolerance to stress that follows bilateral adrenalectomy[206] has led to the conjecture that adrenocortical therapy might enhance resistance to shock, whether or not relative adrenal insufficiency is a factor in its pathogenesis. Clinical studies have produced no convincing evidence in favor of this view.[163] Adrenocortical extract, cortisone and ACTH do not influence the course of experimental hemorrhagic shock that fails to respond to transfusion therapy.[179, 207-210] Occasional patients, however, require adrenocortical therapy. If shock is precipitated by disproportionately mild stress and the eosinophil response is inadequate, adrenal insufficiency should be suspected.[165, 166] There are suggestions that antecedent trauma or debilitating illness may result in a subnormal adrenocortical response to fresh trauma.[9] The bearing of this upon the response to therapy for shock remains to be worked out.

Intra-arterial transfusions. The chief usefulness of intra-arterial transfusions is as a resuscitative measure when the heart has stopped. Blood given intravenously then merely distends the veins and right atrium, whereas an infusion into the arterial tree raises the aortic pressure and forces a flow of blood through the coronary vessels that helps restore cardiac action.[211] Indeed, a pump driving blood into the arterial tree may serve for periods as a substitute for the heart.[212-214] However, in the usual circumstances of shock, there is no convincing evidence that blood replacement is more effective via an artery than via a vein,[121, 215-220] for the cardiac output responds to an increase in venous filling pressure, and this is most directly and most rapidly accomplished by the intravenous administration of blood.[221] The response is a function of the rate of infusion, not the route.[222] Coronary blood flow in experimental hemorrhagic shock improves in proportion to the rise in aortic pressure as cardiac output increases[116] and is improved equally by intravenous and intra-arterial transfusions.[215] A rise in pressure in the left atrium in experimental hemorrhagic shock that is taken as evidence of myocardial weakness is not corrected by intra-arterial transfusion.[134] "Irreversible" hemorrhagic shock produced experimentally in animals with healthy hearts has not been shown to be any more responsive to intra-arterial than to intravenous transfusions.

There are occasions in civilian practice, however, when intravenous transfusions produce increasing congestion without improvement in arterial pressure and a small volume of blood given arterially produces a striking improvement in the circulation. These may be cases of coronary insufficiency due to

shock or myocardial infarction producing shock. Nickerson[222] suggests that the benefit may be attributable to a release of reflex vasoconstriction as the pressure in the aorta and carotid arteries is raised. When hypotension is produced by depression of vasomotor centers or inhibition of peripheral vasoconstriction, as in acute barbiturate poisoning, intra-arterial transfusion fails to elevate the arterial pressure.

Post-traumatic anuria. The histologic appearance of lower-nephron nephrosis suggests that recovery should take place if the patient can be tided over the period of acute uremia and if the primary injuries or disease permits recovery. Successful management of post-traumatic anuria is essential for the ultimate success of therapy of shock.*

"*Irreversible Hemorrhagic Shock*"

"Irreversible" is a term frequently used to describe shock that does not respond to or recurs after blood-volume replacement. Its most precise meaning is given in the hemorrhagic shock experiment, in which it may be considered a shorthand way of saying that the period of severe deficit in blood volume has been prolonged until shock cannot be corrected by the return of all withdrawn blood. The onset of "irreversibility" is not apparent in any observed physiologic or biochemical change. Its probability may be predicted in large groups of standardized experiments, but in individual animals "reversibility" or "irreversibility" is recognized only by the test of blood replacement.

In clinical application the term has been expanded to describe any case of therapeutic failure. So applied it has no usefulness and is better avoided, since it is likely to lead to a neglect of opportunities for therapy. Observers of battle injury state that inadequate blood replacement, continuing or recurring loss of blood or plasma or the development of sepsis can be shown to account for nearly all, if not all, failures to correct shock. Renal injury or coronary or cerebral thrombosis that causes the death of the patient in spite of recovery from shock can be considered forms of "irreversibility," but the term, if used at all, is better reserved to indicate failure to correct the general circulatory collapse.

It is recognized both in military and civilian hospitals that shock responds better to therapy early than late, and that the response to blood replacement after repeated severe hemorrhages becomes progressively poorer than the initial response.

*Measures directed toward the kidney have only occasionally been successful in hastening diuresis. Proper fluid and electrolyte management, particularly the limitation of water administration, prolongs the life of the anuric patient, but in most cases some form of extrarenal dialysis is also required, mainly to prevent potassium intoxication. (Exchange transfusions[204] require quantities of blood that are not available for this purpose in most military or civilian hospitals.) Peritoneal irrigation[205, 206] and extracorporeal dialysis of blood led through cellophane tubes (artificial kidney)[207, 208] have been applied successfully. The artificial kidney dialyzes more rapidly, but requires heparinization, considerable quantities of additional blood and apparatus not generally available. Peritoneal irrigation can be done with materials at hand, but has the drawback of the danger of peritoneal infection. Continuous irrigation for more than forty-eight hours leads to peritoneal contamination with intestinal organisms that migrate through the intact bowel wall.[205, 209] Peritoneal infection can be avoided, however, by limitation of the period of continuous irrigation and by the oral administration of appropriate antibiotic agents.

Hemorrhagic shock unresponsive to blood replacement is readily produced in the laboratory and has been studied extensively to determine the most critical physiologic disturbances that result from prolonged blood-volume deficit. Only a brief outline of the results of these investigations can be given here. As anesthesia, tissue trauma and surgical manipulations are brought to a minimum, the severity and duration of the period of hemorrhagic hypotension required to produce "irreversibility" become marked — for example, an average of four and a half hours (range two to eleven hours) at an arterial pressure of 30 in unanesthetized dogs bled about 50 per cent of their blood volume.[209] The relapse into shock after blood-volume replacement cannot be attributed to recurrence of oligemia,[221] since additional infusions of blood, plasma, albumin or saline or Ringer's solution do not restore blood flow and the addition of glucose or sodium bicarbonate does not add to the effectiveness of infusion therapy.[160]

It has not been established whether the relapse into shock in the presence of a normal blood volume is due to intrinsic failure of the circulatory system or is secondary to a loss of extrinsic controlling mechanisms or to the operation of toxic factors. Correction of disturbed blood chemistry, including azotemia by artificial dialysis, does not correct "irreversible" shock.[222] The correlation of failure of transfusion therapy with persistence of specific intracellular biochemical damage has not yet been accomplished.

Vasomotor tone is maintained in the arterial tree as a whole,[223] although there may be relative dilatation of mesenteric and coronary vessels. Neither pressor therapy (hypertensin, paredrine, nor-epinephrine)[160, 174, 198] nor antiadrenergic or antihistaminic therapy[203] corrects irreversible shock. The hemodynamic pattern in "normovolemic" shock is usually similar to that in "oligemic" shock — that is, the decline in cardiac output is initiated by a decline in venous return,[8, 224-227] in this case presumably owing to stagnation in the capillary bed. A diminished effectiveness of ventricular contraction may also be shown to play a part in some but not all dogs in irreversible hemorrhagic shock.[8, 124, 228] Congestion of the liver and intestine is a regular feature of irreversible hemorrhagic shock in the dog.[229-241] Intrahepatic vasoconstriction persists after blood replacement[242, 243] and may be accompanied by relaxation of mesenteric arterioles.[244] Additional transfusions cause portal hypertension and hemorrhagic exudation into intestinal lumen and peritoneal sac. Impounding of blood in the mesenteric bed does not account for recurrence of shock, however, for an Eck fistula, which bypasses the hepatic blockade, does not prevent irreversible shock.[245]

On direct microscopical examination of the omentum and mesentery of the intestine, Zweifach[85] observed a progressive loss of vascular tone, slowing

of flow and eventually stagnation of blood in the capillary bed. These observations confirm other evidences of "trapping" or stagnation. If this is true of a sufficiently large part of the terminal vascular bed, it explains the decline in venous return to the heart. Shorr, Zweifach et al.[88, 246, 247] believe that these changes in the terminal vascular bed are produced by a humoral vasodepressor material (VDM), which they identify as reduced ferritin, an iron-containing protein, derived mainly from anoxic liver tissue and inactivated by normal liver tissue. But VDM has not been shown capable of producing shock, even in dogs deprived of their ability to inactivate or excrete VDM.[248] Evidence that the liver is involved in the development of "irreversibility" to transfusion in hemorrhagic shock in the dog are the studies from this laboratory showing that "irreversibility" may be prevented or even corrected by the addition of a stream of arterial blood from a normal dog to the portal inflow of the dog in shock.[70, 249] Supporting evidence is offered by Baez, Zweifach and Shorr,[250] who observed that dogs prepared by anastomosis of the renal artery to the portal vein may be bled more severely than control dogs and do not show the decompensatory reactions of the omental capillary bed and that the shock does not become "irreversible."

Markowitz and Rappaport[251] demonstrated that the lethal effect of hepatic-artery ligation in dogs is averted by penicillin therapy. The common factor of hepatic anoxia led to a test of antibiotic protection in hemorrhagic shock.[128] Aureomycin, Terramycin, neomycin and, to a lesser degree, penicillin prevent the development of irreversibility in hemorrhagic shock when given immediately before hemorrhage.[128, 252] The protective action of the antibiotic in hepatic-artery ligation may be due to an inhibition of the clostridia always present in the liver and other tissues of the dog,[66] which are otherwise activated by the tissue anoxia. Recent experiments indicate that the clostridia in liver and skeletal muscle of the dog do increase in numbers or virulence during the course of irreversible hemorrhagic shock.[260] That the clostridia are responsible for irreversibility in shock is doubtful, however, for neomycin, which is strongly protective, is not active against clostridia, whereas immunization with clostridial toxoid or the administration of clostridial antitoxin does not protect.[252] Elimination of external bacterial contamination during the shock experiment does not prevent irreversibility, nor does virtual sterilization of the intestinal canal maintained by closure of the distal divided esophagus after a period of antibiotic feeding.[252] Blood and lymph cultures are sterile during experimental hemorrhagic shock.[252] Comparison of the antibacterial spectrums of antibiotic agents protective in shock with those of antibiotics that do not protect does not point out a bacterial group whose inhibition may be considered to account for the protective effect.[252] Incubation of Aureomycin in solution until all evidence of antibacterial activity in vitro is lost, reduces but does not eliminate its protective action in shock.[252]

The mechanism of the protective action of antibiotics is currently under intensive investigation. Either a subtle bacterial action plays a critical role in apparently "pure" hemorrhagic shock, in the dog at least, or certain antibiotic agents exert undefined nonantibacterial actions capable of preventing the transition from "reversible" to "irreversible" hemorrhagic shock. Antibiotic therapy is not effective if given after experimental hemorrhagic shock has been allowed to become "irreversible."[252]

Shock due to Sepsis

Shock due to trauma becomes increasingly difficult to correct if the injured tissues become infected.[17, 18, 23-26] Severe infection also frequently produces shock in the absence of trauma.[253-255] Shock may be the earliest manifestation of severe infection. Stewart[256] reported cases of streptococcal wound infection in which vascular collapse antedated clinical evidence of sepsis. Similarly, within a two-year period in a civilian hospital, 9 cases of peritonitis were observed in which the abrupt onset of shock so dominated the clinical findings that initial diagnoses were hidden hemorrhage, myocardial infarction or pulmonary embolism.[257] The state of shock undoubtedly reduces the effectiveness of defenses against infection.[258-260]

In the pathogenesis of shock due to infection, reduction in blood volume caused by destruction of red cells and exudation of plasma may play a part, as in peritonitis or clostridial myositis.[16-19, 22] Plasma or whole-blood replacement does not correct shock, however, unless the sepsis is also brought under control.[16-19, 22, 255] The injection of bacteria and bacterial toxins or the toxic products of bacterial action upon protein can produce shock,[47-49, 51, 52, 60, 61, 261, 262] in some cases accompanied by intravascular hemolysis and widespread capillary damage, but in others without reduction in circulating blood volume. Blood volume need not be reduced in shock due to pneumonia or septicemia.[255]

The hemodynamics of shock from sepsis are incompletely known and undoubtedly vary with the nature and phase of the infection. Four phases of response may be recognized after the intravenous injection of typhoid vaccine in human subjects[262, 264]: a *prodromal* period of malaise without objective changes; a *chill* period of fever, vasoconstriction, reduction in cardiac output, slowed circulation time, oliguria and a rise followed by a fall in arterial pres-

*The degree to which even a brief period of shock may reduce antibacterial defenses is shown in recently completed observations upon dogs given suspensions of bacteria (*Escherichia coli*, staphylococci or *Clostridium welchii*) intravenously during or after a two-hour period of hemorrhagic shock (Schweinburg, F., Frank, H. A., and Fine, J. Unpublished data). Although these dogs recovered from shock in response to replacement transfusion, all subsequently died of widespread growth of the injected organisms, in contrast to normal dogs, which regularly cleared the blood stream and tissues of similar doses of bacteria. Normal antibacterial defenses were not regained for forty-eight hours after the period of shock.

sure, which may reach severely hypotensive levels; a *flush* phase of vasodilatation, profuse sweating, marked rise in cardiac output, acceleration of circulation time and recovery of arterial pressure, sometimes after a further initial fall; and a *defervescence* phase in which the circulation returns to normal. The blood volume does not change during this reaction. The circulatory adjustments during the chill phase are much like those of wound shock, but the blood volume is normal and the episode is self-limited. Lethal circulatory collapse may be produced in dogs by the injection of minute quantities of the toxin of the Shiga bacillus.[52] The cardiac output falls drastically and progressively, and total peripheral resistance rises sharply, delaying the fall in arterial pressure. Central venous pressure falls, but portal venous pressure may rise, presumably because of intrahepatic venoconstriction. Blood volume is not reduced. In shock due to peritonitis, plasma volume falls in consequence of intraperitoneal exudation. In one group of these experiments,[265] plasma-volume replacement restored cardiac output, but the arterial pressure remained low and the dogs did not survive. This evidence suggests the action of a bacterial toxin upon peripheral vessels or medullary centers.[265] Possible adverse influences of bacterial toxins upon all elements of the cardiovascular apparatus have been suggested.[265, 266]

From the therapeutic standpoint, major dependence is placed upon antibiotic therapy and surgical measures for control of sepsis. Clinical guides to the degree of blood-volume reduction have not been worked out as for wound shock. The value of transfusions beyond those required to correct volume deficits is debatable. Pressor drugs may be of value when vasomotor activity is deficient. As the period of sepsis becomes extended, dehydration, electrolyte loss, malnutrition and anemia become important factors, and the question of adrenocortical depletion arises.

Shock due to Myocardial Infarction

About 10 to 15 per cent of patients with myocardial infarction manifest clinical signs of shock — for example, a fall in arterial pressure, pallor and moistness of the skin of the face, coldness and pallor or cyanosis of the skin of the extremities, constriction of the superficial veins of the extremities and of the radial artery, small amplitude of the radial pulse and oliguria or anuria.[267, 268] In these patients the mortality rate is increased to 80 to 90 per cent or higher, from the mortality rate of 20 to 40 per cent* in myocardial infarction without shock.[267, 268, 270, 271] Shock here is due to disease of the heart, although its clinical manifestations may be indistinguishable from those of "peripheral" vascular collapse.

Boyer,[272] in 1944, reviewed efforts to demonstrate the nature of hemodynamic disturbance in "cardiogenic" shock. These were hampered by inadequacy of the methods applied for the measurement of cardiac output in patients[273] and by failure to produce shock by coronary-artery ligation in dogs.[274] Loss of myocardial contractility — indeed, dilatation of the ischemic portion of the ventricle during systole — has been demonstrated after coronary-artery ligation in the dog,[275, 276] but the consequent decline in cardiac output[274] is presumably limited in the dog by increased performance of the stretched nonischemic myocardium.[276] The arterial pressure is maintained, indicating an increase in peripheral resistance.[276] More recent studies have demonstrated similar mechanisms in man. Among 11 patients with myocardial infarction,[277] the average cardiac output by the Hamilton-dye method was found to be 3.4 liters per square meter per minute in the absence of shock and 1.8 liters when clinical signs of shock were present. Average stroke volume was 50 cc. in the former group and 27 cc. in the latter. The average calculated peripheral resistance (2050 dynes cm.$^{-5}$ sec.) and circulation time (45 sec.) in the group in shock were nearly double those values in the group without clinical evidences of shock. Blood volume and central venous pressure were not reduced in the shock group. Reduction in cardiac output and absence of significant reduction in blood volume have been confirmed in other clinical studies of shock due to myocardial infarction.[278, 279] The current concept, then, is that reduction in cardiac output is due to loss of contractile strength of the ventricle in hearts that cannot compensate by improved performance of the nonischemic myocardium. The consequent fall in arterial pressure initiates compensatory vasoconstriction as in other forms of shock. Other factors may play a part. Paroxysmal tachycardia or arrhythmia further reduces cardiac output. Some cardiac patients show marked hypotension when given morphine.[280] Pulmonary edema adds the factors of plasma loss into the lungs and arterial anoxia. It does not seem necessary to postulate the initiation of adverse neurogenic impulses or the absorption of toxic products from the ischemic myocardial tissue. Indeed, as Ebert and Stead[281] have emphasized, shock is a common terminal event in congestive heart failure due to any form of heart disease. In such patients blood volumes and central venous pressures are usually above normal, and the signs of "peripheral vascular collapse" coexist with those of congestive heart failure.[281] A somewhat similar situation may be produced by overtransfusion of the dog in "irreversible" hemorrhagic shock.

The hemodynamic disturbance sets up the dilemma that therapy successful in improving peripheral blood flow and coronary blood flow increases the work load of the heart. Measurements are not available to determine the net effect of the increase in coronary blood flow produced by transfusions or pressor drugs in patients with coronary-artery dis-

*The mortality rate of myocardial infarction is considerably lower in patients who do not require hospitalization.[269]

ease in relation to the circulatory requirement of the myocardium at the increased work level. Nor is it clear to what extent efforts must be made to sustain peripheral circulation at the expense of increased strain upon the heart. However, there is clinical evidence that recovery from shock due to myocardial infarction is accompanied by improvement in the general condition of the patient and no increase in congestive heart failure.

Transfusion therapy has been tested because the clinical signs of "peripheral circulatory failure" respond so dramatically to transfusion therapy in traumatic shock. In general, the mortality rate has not been reduced thereby.[280, 282] Individual patients, however, are improved strikingly, although a number subsequently relapse into shock and do not respond to further transfusion therapy. Transfusions are usually given cautiously, and overt pulmonary congestion or edema is not produced. Intra-arterial transfusion occasionally improves arterial pressure and cardiac function and reduces pulmonary congestion when intravenous transfusions are ineffective.[283-285] Data are not given on blood volume, cardiac output or peripheral resistance to help select patients for transfusion therapy or determine an optimal rate and volume or route.

Pressor therapy has been tested, in the hope of improving blood flow through coronary and cerebral vessels. Direct measurements of these effects in relation to the influence on the work of the heart are not available. Arterial pressure is usually raised for considerable periods. The effect on survival is not yet established.[196, 287] Peripheral resistance falls in an occasional patient with myocardial infarction, [278] and the recognition of such cases should lead to a useful application of pressor therapy. In general, however, pharmacotherapy is directed at improving the function of the heart.[279] An optimistic report in this regard is that small doses (0.5 microgm. per kilogram of body weight) of nor-epinephrine (but not of epinephrine) restore the intramyocardial oxygen tension after coronary occlusion in the dog, without increasing the mean arterial pressure to a significant degree and without producing ectopic beats.[286] The most recent account of vigorous transfusion and pressor-drug therapy for severe shock due to myocardial infarction reports that 14 of 32 patients recovered although each had been considered almost certain to die.[287] In several of these patients pulmonary edema cleared as shock was corrected.

Summary

The development of shock due to injury is determined by the degree of loss of whole blood or plasma from and into the injured tissues. Cardiac output falls as a result of failure of venous return. Peripheral vessels constrict in response to the fall in intravascular pressure. The clinical signs of shock supply a good index of the degree of blood-volume deficit and the adequacy of replacement therapy. During the period of shock, all tissues suffer the effects of a progressive deficiency in blood flow. Functional insufficiency of critical organs such as the kidneys and the liver adds to the over-all disturbance. Therapy is directed at the interlocked problems of blood-volume replacement and surgical management, which aims at terminating blood loss, halting bacteria invasion and setting the stage for healing of the injured tissues. When this can be accomplished, the widespread physiologic and biochemical disturbances are almost always corrected. However, renal injury, coronary thrombosis or other critical damage occurring during the period of shock may subsequently cause the death of the patient. Older patients with pre-existent visceral and vascular disease do not respond as well as young men to delayed blood replacement.

Shock also occurs in the absence of significant oligemia. Invasive infection is the usual cause of relapse into shock of the injured patient whose blood deficit has been replaced and who has not bled anew. Severe sepsis also produces shock in uninjured patients. Clinical signs of sepsis may be overshadowed by the vascular collapse. Success in therapy depends primarily upon control of the sepsis, but is favored by concurrent measures that sustain the circulation. Therefore, detailed investigation of the various adverse effects of bacterial infection upon the cardiovascular apparatus is in progress. Similarly, the outcome in shock produced by myocardial infarction is determined by the possibility of functional recovery in the damaged myocardium and coronary tree, but this in turn depends in part upon the success of efforts to sustain the circulation during the recovery period. The special therapeutic problem posed when shock is primarily due to inadequacy of the heart is that the strain upon the heart is increased by measures that improve the peripheral circulation.

For the control of shock due to injuries and blood loss, the major effort lies in the areas of procurement, preservation, transportation and safe administration of whole blood and plasma, development of substitutes for plasma and organization of services to integrate blood replacement with the remainder of the surgical management of the wound and the patient. From the standpoint of physiologic investigation, the most challenging problems lie in the working out of hemodynamic and biochemical disturbances and opportunities for therapy in states of shock not primarily due to blood-volume deficit or not responsive to blood-volume replacement.

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MEDICAL INTELLIGENCE

SYMPTOMS OF DEPRESSION IN CARDIAC FAILURE

Report of a Case

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THE case reported below concerns a patient who, during a period of intense emotional stress, had signs and symptoms of organic disease that were diagnosed as purely functional because of the emotional background.

CASE REPORT

B. B., a 43-year-old spinster, was first seen by a psychiatrist (D. J. F.) on February 27, 1953, with the chief complaint of extreme nervousness.

She stated that her symptoms had begun approximately 2 years previously, when her father, to whom she was strongly attached, suffered a stroke. She gave up her work to care for him and manage their home. The mother was also ill at the time, suffering from a senile psychosis, and was being cared for at home. Because her father was frequently disturbed at night, the patient lost considerable sleep and became increasingly more nervous and depressed. She consulted her family physician, who knew of the situation, and he advised her to return to work. At the same time he prescribed Dexamyl. She followed his advice and claimed to have felt slightly better for a short time. Within 2 months of her return to work her father died, and she again had to give up her job because of a marked increase in her symptoms. She consulted other physicians, all of whom told her that her condition was due to nervousness. Because of this she finally decided to seek psychiatric help.

Examination revealed a tense, anxious, moderately depressed woman who appeared older than her stated age. When questioned about her complaints of nervousness, she stated that she was extremely tired, became exhausted with the slightest exertion, frequently had shortness of breath, often occurring at night, and was frequently awakened by frightening dreams. During the interview she cried a great deal, particularly when discussing her father's illness and death. It was only with a considerable effort that she was able to control her emotions. Despite her depression, no suicidal ideas were elicited nor was there any disturbance in thinking.

The history of gradually developing symptoms during a period of intense environmental stress and her clinical picture suggested a functional illness. However, the complaints of dyspnea and terrifying dreams were highly suggestive of cardiac disease, so that same afternoon the patient was examined by an internist.

On careful questioning she gave a definite history of squeezing, substernal pain, with radiation to both shoulders on physical activity and transient episodes of shortness of breath, often waking her from sleep at night. There was orthopnea requiring 2 pillows for relief. She also noted palpitation of the heart, with irregular heart beat. These symptoms went back about a year and a half, during which she had been checked by 4 physicians, who told her that she had a heart murmur of no particular consequence.

The height was 5 feet, 1 inch, and the weight 129 pounds. The positive physical findings included slight cyanosis of the mucous membranes, distention of the neck veins and + ankle edema. There were rales at both bases. The heart was enlarged, the border of cardiac dullness extending almost to the left axillary line on percussion and palpation. The heart rate was 96, with frequent extrasystoles. There was a Grade 2 palpable thrill at the base in the aortic area. All over the precordium a Grade 3 rough systolic murmur could be heard; this was maximal in the aortic area at the base to the right of the sternum. No other murmurs were audible. There was no audible aortic second sound. The liver edge was palpated 5 cm. below the right costal margin and was slightly tender.

An electrocardiogram showed a rate of 96, with frequent ventricular extrasystoles. The T waves were sharply inverted in Leads 1 and 2 and also in the precordial Leads 4 and 5.

A diagnosis of aortic stenosis, with failure of the left ventricle and angina pectoris, was made. The patient was put on restricted physical activity. She was given digitalis, a low-sodium diet, nitroglycerin for chest pain and phenobarbital for nervousness.

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Arrangements were made to relieve her of the care of her senile mother.

She was seen again on March 6 and March 20, 1953, when she had lost 9 pounds. The pulse was 78 and regular, with infrequent extrasystoles. The lungs were clear. The liver edge was not palpable. She had no more chest pain and no more paroxysmal dyspnea. She was maintained on daily doses of digitalis and phenobarbital. There was a concomitant improvement in her emotional status as well. She no longer presented the picture of anxiety, tension or depression. She was pleasant, cheerful and most appreciative of her treatment. She was planning to return to work on a part-time basis.

Discussion

This case is considered to be of interest because it points out several fundamental concepts in diagnosis and treatment. In the first place, a carefully conducted physical examination is still of paramount importance; the patient's previous physicians either failed to take this consideration into account or were completely misled by the functional nature of the complaints. Secondly, all symptoms should be carefully evaluated. Finally, and probably most important, psychiatry is a medical specialty; therefore, psychiatric treatment must not be left to those who are untrained in medicine. This patient could easily have been carried on for a prolonged course of psychotherapy, with disastrous results.

154 Waterman Street

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

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CASE 39381

Presentation of Case

A fifty-one-year-old housewife was admitted to the hospital because of the sudden onset of vomiting, unresponsiveness and paralysis of the right arm and leg.

Her husband said that she had been well, though obese, until ten years before admission, when she had an episode of vomiting and collapse and was taken to a hospital, where she was told that she had pneumonia and a nervous breakdown. No paralysis was noted, but afterward she was less energetic and tired more easily. Eight years before admission she was hospitalized because of sudden right-sided paralysis. This gradually cleared over several weeks, with little residual weakness. Five years before admission she was given digitalis because of dyspnea. Recently, she had been taking 1 pill of digitoxin daily. Three years before admission right-sided paralysis again suddenly developed, decreasing gradually for several weeks but never entirely clearing. Since that time she had been childish, never regaining her former personality. One year before admission exertional dyspnea became severe, and nocturnal dyspnea, ankle swelling and "swollen neck veins" were noticed for the first time. She was hospitalized for "palpitations," and at that time diabetes was discovered. Glycosuria had been controlled by diet, and she had lost 20 pounds in the past year, attributed to the diet. During this hospitalization she was given nitroglycerin tablets for infrequent pain in the anterior aspect of the chest, always with prompt relief. The chest pain was unrelated to exertion. At the onset of paralysis sixteen hours before admission she vomited and became unresponsive and incoherent. Dyspnea increased and she perspired profusely.

Physical examination disclosed an acutely ill, stuporous, cyanotic, tachypneic, somewhat obese woman who was moaning constantly. The neck veins were distended but not pulsating. There were scattered moist rales over the lung bases posteriorly. The cardiac apical beat was felt 11 cm. to the left of the midsternal line in the fifth intercostal space. There was auricular fibrillation, with a ventricular rate of 160. There was a questionable diastolic gallop at the apex. The heart sounds seemed to be of normal intensity, but they were partly obscured by noisy breathing; the aortic second sound equaled the pulmonic. The liver border was firm and smooth, extending four fingerbreadths below the lower costal border. There was ++ pitting edema of the ankles and sacrum. The right radial, right femoral and both pedal pulses were not palpable, but the extremities were warm.

Neurologic examination revealed loss of left lateral gaze. The corneal reflexes were present. The pupils were equal and did not react to light. The fundi were normal. There was questionable ptosis of the right lid and questionable flattening of the features on the right side of the face. The tongue was in the midline. Gag reflex was present. There was no response to pinching. There was complete flaccid paralysis of the right arm and leg. Deep tendon reflexes of both arms and legs were absent. The Hoffmann reflex was ++ on the right and absent on the left. The right plantar reflex was absent, the left flexor.

The pulse was 160, the temperature 100.2°F. by rectum, and the respirations 40. The blood pressure

was 105 systolic, 90 diastolic. The weight was approximately 130 pounds.

The urine was cloudy, orange and acid and gave a ++++ test for albumin, a green test for sugar and a + to ++ test for bile; the sediment contained 8 to 10 white cells, 0 to 1 red cells, occasional hyaline, granular and red-cell casts and many bacteria per high-power field. The white-cell count was 16,900, with 85 per cent neutrophils, 14 per cent lymphocytes and 1 per cent monocytes; the hemoglobin was 18 gm. per 100 cc., and the hematocrit 60 per cent. The fasting blood sugar was 236 mg. per 100 cc., the prothrombin time 40 per cent, the nonprotein nitrogen 44 mg. per 100 cc., and the sodium 138 milliequiv., and the chloride 108 milliequiv. per liter. A lumbar puncture revealed an initial spinal-fluid pressure equivalent to 230 mm. of water; 15 cc. of clear colorless fluid was removed, and the final pressure was equivalent to 180 mm. of water. The fluid contained 4 lymphocytes, 1 neutrophil and 12 red cells per cubic millimeter. The ammonium sulfate test was negative.

Two hours after admission the patient vomited about 20 cc. of coffee-colored material, which had a +++ guaiac reaction. On the next day she was still unresponsive and had begun to sweat profusely. The blood pressure was 85 systolic by palpation. The pulse was 80, and there was still auricular fibrillation. The temperature was 102.5°F. by rectum. Moist rales at the lung bases were more prominent. There was a distinct diastolic rumble at the apex. Later that day the blood pressure and pulse became unobtainable, and cyanosis deepened; the respiratory effort grew weak, and the heart rate slowed to 40 per minute. The right pupil was larger than the left, and both reacted sluggishly to light. The eyes moved in all directions when the head was moved. The patient died shortly after examination, forty-two hours after admission.

Differential Diagnosis

Dr. Briant L. Decker*: In summary, this fifty-one-year-old woman, in the eight years before admission to the hospital, had had three cerebrovascular accidents, and in the previous five to ten years had evidence of congestive heart failure. She entered the hospital in her terminal illness in coma with a right hemiplegia and congestive heart failure.

There are several interesting possibilities to explain this train of events. I can be sure that she had rheumatic heart disease with mitral stenosis. I base this opinion on the apical diastolic rumble heard terminally, the presence of auricular fibrillation and the long history of congestive heart failure, at least for five and possibly for ten years. With this diagnosis as a basis, it might be assumed that the auricular fibrillation was of at least eight years' duration and that the cerebrovascular accidents of eight and three years previously were on an embolic basis. The characteristics of suddenness of onset of both attacks and practically complete recovery from the first attack and fairly good recovery from the second fit in with embolic phenomena. The fact that she never regained her former personality after the second cerebrovascular accident is consistent with that explanation. It is reasonable to suppose that the final apoplectic attack was also embolic and that a large portion of the left middle cerebral artery was involved. The normal spinal fluid is against cerebral hemorrhage, although the terminal events suggested increase of intracranial pressure; likewise, the absent pulsations in the peripheral arteries may be explained by emboli from the left atrium.

The bile in the urine, the prothrombin time of 40 per cent and the urinary findings could have been the effect of chronic congestive heart failure on the liver and kidneys, but I doubt if the hemoglobin of 18 gm. and the hematocrit of 60 per cent can be explained by congestive heart failure due to mitral stenosis. I believe the most likely possibility is that the patient also had tricuspid stenosis. A typically localized murmur was not described, but it is often indistinguishable from that of mitral stenosis and, of course, the two occur together.

Could the cerebral episodes and the bouts of congestive heart failure have been due to polycythemia vera? Against this explanation is the absence of an enlarged spleen. I should think that with polycythemia vera of this duration the hemoglobin and hematocrit would have been at a higher level. I believe the polycythemia was secondary.

Since the patient had diabetes, might it not be reasonable to suppose that, in addition to the mitral stenosis, she had considerable arteriosclerosis and that the absent pulsations in the extremities and at least the final cerebrovascular accident were on an arteriosclerotic basis, and that the terminal coma and hemiplegia were due to progressive thrombosis? Furthermore, she had pain in the anterior aspect of the chest relieved by nitroglycerin so she may have had a myocardial infarct as the cause of the final terminal congestive heart failure, which produced cerebral thrombosis by precipitating a marked drop in blood pressure. Against these explanations are the facts that the diabetes was mild and was controlled by diet, that the fundi were reported as being normal, that the sudden onset of the final cerebrovascular accident is more suggestive of an embolus or hemorrhage than of thrombosis, that there was no history of chest pain before the paralysis and that no electrocardiogram was mentioned in the protocol although I am sure a tracing was taken so it must not have been significant.

It seems to me that, with the duration of the history, a brain tumor is unlikely as an explanation of the cerebral symptoms.

Summing up, I believe that this patient had rheumatic heart disease with mitral stenosis and auricular fibrillation, giving rise to cerebral and

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possibly to peripheral emboli. Recently, I have seen a case and been told of another in which there were absent pulsations in the extremities in association with a cerebrovascular accident and congestive heart failure. The explanation of this was not clear, but it was suggested that it was on a sympathetic basis. This patient probably had tricuspid stenosis. I am not sure of the order in which the terminal events occurred, but I believe that before admission she was in congestive heart failure, was fibrillating and had a fairly large embolus lodged in the left middle cerebral artery, which produced right hemiplegia and coma. I am sure she was digitalized on admission, but the heart failure, together with the indirect effects of the cerebral accident, caused her death. I suppose that she may have had a ball-valve thrombus in the left atrium, but I should think that there would have been more evidence of shock earlier than occurred and besides there was adequate reason for her death without my postulating this. She may well have had one or more pulmonary emboli, but I have nothing specific on which to justify this except perhaps the vomiting of guaiac-positive material, which may have been due to blood swallowed but was more probably caused by marked congestion of the abdominal viscera.

DR. JOSEPH C. AUB: I should be puzzled by the same paralysis three times in a row. Does there not have to be something local like a hemangioma or an aneurysm that just keeps on oozing to do that?

DR. DECKER: I think that is a good possibility; however, I have tried to put it all on one diagnosis rather than break it up.

DR. JOHN B. STANBURY: Since the patient had repeated paralysis on the right side, the service entertained the possibility that she had the syndrome of intermittent internal carotid occlusion. We also considered the possibility that bacterial endocarditis accounted for the cerebral emboli. Our final impression was much as Dr. Decker has outlined, but I do not think we included tricuspid disease. We thought the polycythemia was secondary.

DR. JACOB LERMAN: Why were the left tendon reflexes absent?

DR. EDWARD P. RICHARDSON, JR.: We have no explanation for this finding.

DR. LERMAN: Why was there no aphasia during all this time? Was she left-handed or right-handed?

DR. RICHARDSON: She was right-handed.

A PHYSICIAN: How often does one see polycythemia in conjunction with a hemangioma?

DR. BENJAMIN CASTLEMAN: It is seen only if it occurs in the lung as an arteriovenous aneurysm. There has to be a left-to-right shunt to produce polycythemia. I do not believe it is seen with hemangiomas in the brain.

CLINICAL DIAGNOSES

Thrombosis of left middle cerebral artery.
Arteriosclerotic heart disease, with auricular fibrillation and congestive heart failure.
Gastrointestinal bleeding.
?Polycythemia vera.

DR. BRIANT L. DECKER'S DIAGNOSES

Rheumatic heart disease, with mitral stenosis and auricular fibrillation.
Cerebral and ?peripheral emboli.
Embolus to left middle cerebral artery.

ANATOMICAL DIAGNOSES

Rheumatic heart disease, with mitral and aortic stenosis.
Mural thrombosis, left atrium, with recent emboli to right internal carotid and superior mesenteric arteries.
Cerebral infarcts, recent and old.
Thrombosis, old, probably embolic, of abdominal aorta.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At the time of autopsy we found an enlarged heart weighing 500 gm., and, as suggested by Dr. Decker, the patient did have rheumatic heart disease with a stenotic button-hole type of mitral valve. There was also aortic stenosis, not calcified, but with sufficient fusion of two cusps to produce a bicuspid aortic valve. The tricuspid valve was normal. There were mural thrombi in the left atrium, most of them quite well healed, but attached to some of the healed ones were fresher thrombi that apparently were the site of the recent embolic phenomena. We found evidence of old embolic episodes to the kidneys and spleen. The abdominal aorta below the level of the renal arteries was almost completely occluded, and may have been the site of an old embolus, which had organized, with superimposed thrombus; this had extended into the right iliac artery, explaining the lack of pulsation in the leg. We also found an embolus in the superior mesenteric artery that was quite fresh and apparently had not produced any change in the bowel at the time of autopsy. I do not know how recently this had occurred. The liver showed marked congestion, but there was no evidence of cardiac cirrhosis.

I shall leave the description of the brain to Dr. Richardson.

DR. RICHARDSON: As sometimes occurs, we found more lesions in the brain than can be accurately correlated with the clinical symptomatology.

The location of the cerebral lesions is illustrated in a diagram (Fig. 1). A large scar, typical of old infarction, was found on the orbital surface of the left frontal lobe, and a similar, but smaller infarct was located in the corresponding area on the right.

The cortex and immediate subcortical white matter had been destroyed in these areas. On sectioning the brain we found additional old infarcts independent of those seen on the surface. One of these involved the left putamen and a portion of the left internal capsule, and encroached upon the insula. Another, on the right, had destroyed the lateral aspect of the putamen. In addition to these old infarcts, there were several recent foci of infarct necrosis, partly hemorrhagic and partly ischemic. These were found in the inferior aspect of the left cerebellar hemisphere, in the cerebral cortex in the left parieto-occipital region and on the medial aspect of the left cerebral hemisphere in the central (Rolandic) region.

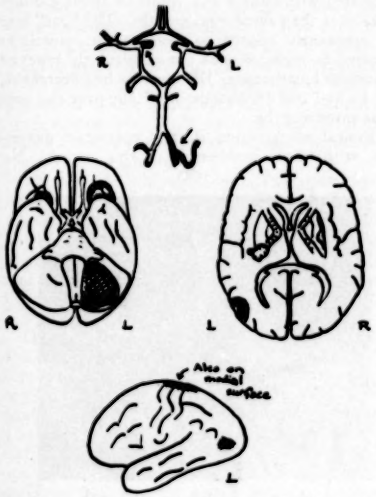

FIGURE 1. *Diagrammatic Views of the Circle of Willis and of the Brain.*

The arrows indicate the occlusion of the right internal carotid artery and the recent embolus in the left vertebral and posterior inferior cerebellar arteries. Old areas of cerebral infarction are outlined by diagonal lines, and recent infarcts are shown by cross-hatching.

The cerebral arteries were free of atherosclerosis. The intracranial portion of the right internal carotid artery was totally occluded by light-yellowish-brown material, representing an old thrombus. No visible occlusions were found in the left internal carotid artery or its major branches. The left vertebral and posterior inferior cerebellar arteries were distended and completely obstructed by recent, ante-mortem blood clot. The absence of disease of the cerebral arteries and the obvious source for emboli are evidence strongly in favor of an embolic basis for the vascular lesions in the brain.

It seems probable that the initial episode of transitory right hemiparesis was the result of the lesion in the left orbital frontal cortex, which was so placed as to have no permanent effect on the motor pathways. The persistent right hemiparesis, which appeared five years after the previous "stroke," undoubtedly resulted from the lesion in the left internal capsule. There were no definite neurologic signs that could be related to the old infarcts of the right cerebral hemisphere, but the report in the history that the patient never regained her former personality may well have been related to the presence of bilateral orbital frontal lesions. The absence of aphasia is explained by the fact that the areas necessary for the organization of speech were intact, for the lateral frontal, parietal and temporal lobes were not involved in these lesions.

The terminal right hemiplegia was undoubtedly the result of the recent cerebral infarction, the largest part of which was due to occlusion of the left vertebral and posterior inferior cerebellar arteries. This embolus, in addition to producing a large lesion in the cerebellum, obstructed the blood supply to the left lateral aspect of the medulla oblongata and lower pons. A vascular insult of this kind frequently results in worsening of a hemiparesis residual from a previous lesion, apart from any effect it may have had on the long motor tracts descending in the pyramid. It is of interest that the patient terminally had a paralysis of left lateral gaze, which is well explained by the interruption of the blood supply to the pontine center for lateral conjugate deviation of the eyes, located in the vicinity of the abducens nucleus.

CASE 39382

PRESENTATION OF CASE

First admission. A fifty-eight-year-old man entered the hospital because of "indigestion."

About six weeks previously he experienced three attacks of "tight-pressure" type, nonradiating, subxiphoid pain. There was no associated nausea, vomiting or sweating. The first two attacks were mild and relieved by sodium bicarbonate and rest. The third attack came on twenty minutes after the drinking of a milk shake, was severe and lasted about three hours. X-ray films were said to have shown gallstones. He was placed on a low-fat diet and had no recurrence of symptoms. He was referred to the hospital because of a questionable gastric lesion seen on the x-ray film.

Twenty-five, four and two years respectively before admission the following operations were performed: an appendectomy, lysis of adhesions that had caused intestinal obstruction and a left nephrectomy because of kidney stones. He had had inter-

mittent attacks of gouty arthritis for about nine years before admission.

Physical examination was unremarkable except for the scars of the previous operations.

The temperature, pulse and respirations were normal. The blood pressure was 150 systolic, 100 diastolic.

Urinalysis was negative. The hemoglobin was 17 gm. per 100 cc. and the white-cell count 9000. The blood chemical determinations were normal. A Graham test revealed a solitary gallstone. A gastrointestinal series showed marked deformity of the duodenal cap, with thick edematous mucosal folds within which two active ulcer craters were present. An intravenous pyelogram demonstrated

FIGURE 1. *Upper Gastrointestinal Examination. Arrows point to the smooth, rounded defect within the duodenal bulb.*

a normal right kidney. An electrocardiogram revealed T-wave changes consistent with coronary-artery disease.

The patient was placed on a bland diet with interval feedings of Amphogel with belladonna and discharged on the fifth hospital day.

Second admission (two and a half months later). In the interval further x-ray studies had demonstrated findings consistent with prolapse of an antral polyp into the duodenal bulb (Fig. 1 and 2). On the first hospital day a cholecystectomy and gastrotomy were done, with excision of a gastric polyp. The gall bladder contained numerous stones, all larger than the diameter of the lumen of the cystic duct. The bile ducts were free of stones. The x-ray finding of an antral polyp that had prolapsed into the duodenum was confirmed. The stomach was otherwise grossly normal except for slight thickening at the site of the polyp. A segment of gastric wall 4 by 1.5 cm. including the polyp was resected. Microscopical examination of the specimen of stomach showed adenocarcinoma in situ; it could not be determined how much resection margin was obtained. The postoperative course was unremarkable.

Third admission (three years later). The patient was admitted with an attack of gout. A gastrointestinal series revealed a narrowed area of mucosa extending from the shortened antrum to what was a constantly deformed and narrowed duodenal cap. This was thought to be secondary to the previous operative procedure.

Fourth admission (two years later). For the previous year and a half he had had epigastric "gas," associated with nausea and vomiting about a dozen times over the past several months. The "gas" was not constantly related to food and it sometimes occurred at night; it was not consistently relieved by sodium bicarbonate. His appetite had decreased, and he had lost 16 pounds in weight over the previous three months.

Physical examination showed epigastric distention, with slight tenderness in this region. No

FIGURE 2. *Spot Film of the Distal Stomach and Duodenum. Arrows point to the defect, which is now within the gastric antrum.*

masses were felt. Otherwise, the examination was as before.

Examinations of the blood were normal. The urine gave a + test for albumin, and the sediment contained 4 red cells, 3 white cells, rare uric acid crystals and a moderate number of bacteria per high-power field. The stool guaiac test was negative. Free hydrochloric acid was present in the gastric secretions. Cytologic examination of gastric fluid was unsatisfactory. A gastrointestinal series showed a large amount of fluid in the stomach even though the patient had fasted for twelve hours. There was a deformity of the antrum at which point there was complete obstruction. The distal part of the filled portion of the antrum had a sharp, shelf-like border.

On the seventh hospital day an operation was performed.

Differential Diagnosis

Dr. Frank E. Wheelock, Jr.*: Before the first admission the patient had a tight, pressure type of subxiphoid pain. If this had been due to disease of the gall bladder characteristically the pain might have been described as one that came on suddenly, increased at a steady progressive rate until it reached its maximum severity and then remained constant until it either passed off or was relieved. But, of course, there are many variations of the characteristic pattern of gall-bladder pain. This type could also have been somewhat atypical pain from the two duodenal ulcers, particularly because it was relieved by soda; it is hard to explain, however, why the ulcer pain lasted for three hours unless there were definite complications. The third condition that could have caused this pain is prolapse of the mucosa through the pylorus. Another possibility is that the pain was in some way related to the heart. There is evidence that the patient had heart disease with slight hypertension and T-wave changes that, I gather, were definitely indicative of some coronary problem.

The stone in the left kidney, I imagine, was related to the gout; from 10 to 30 per cent of patients who have had gout for any length of time are reported to have trouble in the kidneys in the nature of nephritis or definite urate stones. This apparently had no bearing on the further trouble. The laboratory data are not very helpful.

May I see the x-ray films?

Dr. Joseph Hanelin: It is very easy to confuse the deformity of the duodenum resulting from ulceration and that from prolapse of gastric mucosa or even a gastric polyp into the duodenum; we have made errors both ways in that type of situation. The initial films five and a half years before the last admission and immediately before the first operation show a defect that alternates between the duodenal bulb and the gastric antrum. I seriously question whether there was at any time actual ulceration of the duodenum. Certainly, in films when the mucosa had apparently fallen back into the stomach, we see a bulb of perfectly normal contour. Here is a defect within a duodenum of fairly normal contour that might well be regarded as a polyp (Fig. 1); here the defect seems to have come back into the stomach itself (Fig. 2). Films three years later demonstrated changes incident to surgery. Presumably a sleeve resection of the stomach was done, with anastomosis of the proximal duodenum and the gastric antrum. There is slight irregularity along the distal margin of the antrum in this area that could be entirely due to surgery. When the patient was seen five and a half years after the first admission, about two years after the postoperative film, almost complete obstruction was observed at the gastric antrum. This irregularity along the free margin of the antrum strongly suggests shelf formation.

Dr. Benjamin Castleman: I do not believe that the report in the summary of the first operation is clear. No polyp was found in the specimen resected from the gastric wall during the second admission. The mass proved to be herniated mucosa rather than a true polyp. It was this mucosa that showed carcinoma in situ.

Dr. Wheelock: As I understand it, of the three diagnoses mentioned in the protocol only one is left; the patient did not have a polyp and did not have a demonstrated ulcer crater.

Dr. Hanelin: I should rule out duodenal ulceration. Apparently, he had no polyp; the defect that we saw was entirely due to prolapse of the mucosa through the pylorus.

Dr. Wheelock: We might classify the type of operation. Did the surgeon do a sleeve resection, or did he merely take out a piece of the wall?

Dr. Castleman: He took out a piece of the wall with the lesion in it.

Dr. Wheelock: One part of the wall was left — perhaps three quarters of the circumference.

During the second admission two and a half months later, there was no mention of further symptoms so I gather that he entered the hospital because of the x-ray picture that was worrisome to his physician. We have just seen the x-ray films taken during the second admission that led to the operation. At the time of operation, apparently, the surgeon realized that the duodenal ulcer was not the main problem and elected not to treat it, probably because the radiologists had not actually demonstrated a crater as they thought they had. He elected to remove the gall bladder and this polyp or bit of redundant mucosa. One would hate to do a subtotal gastrectomy and cholecystectomy at the same time, particularly in this patient, who was handicapped by heart disease, had only one kidney and so forth, so that I am sure that the surgeon did not consider a subtotal gastrectomy and cholecystectomy, which, of course, would have completely cured all the diseases I originally thought he had — namely polyp, ulcer and gallstones. Another choice might have been a subtotal gastrectomy to get rid of the polypoid trouble and whatever else was around the duodenum and either to leave the gallstones to a later day or to do a cholecystostomy and remove the gallstones; that would be a reasonably safe operation. I am sure that the decision that was made at the time was the correct one and that ordinarily the patient would have done very well. No one could, of course, have foreseen the finding of carcinoma in situ. The size of the piece of tissue removed was 4 by 1.5 cm. This would lead one to believe that its width was perhaps not adequate. It has been our experience that removed tissue shrinks so much that unless it is stretched a great deal in the laboratory, the laboratory's measurements do not provide an accu-

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rate in vivo figure of how much tissue is actually removed. I imagine that the width may have been as much as 2.5 cm. at the time it was removed.

The third admission concerns me little since it was for gout. X-ray films were repeated; the radiologists could not tell that anything had changed very much; there was the scar thought to be due to operation.

The fourth admission was for serious trouble. For a year and a half the patient had been having gas pains that were not relieved by sodium bicarbonate and not related to eating; for several months he had been vomiting, but only twelve times in all, and he had lost 16 pounds in three months. These symptoms could certainly be those of obstruction of the duodenum or the antrum shown in the x-ray films. Apparently, the obstruction was not complete for a long time or he would have vomited more. On examination the epigastrium was tender and distended; it does not mention whether a splashing sound could be heard when the upper abdomen was jiggled — a very good test to determine clinically whether there is obstruction in the stomach region.

About the laboratory reports, the urinary findings could easily have been due to uric acid deposits in the kidneys, or to pyelonephritis. The stool guaiac test was negative. Even if this had been carcinoma, I do not think that would be significant. That free hydrochloric acid was present in the stomach is perhaps a point against a diagnosis of cancer since in 75 per cent of patients with cancer of the stomach, free acid is not present according to some authors.

The cytology is reported as being unsatisfactory, which I think means negative because the tumor cells were not seen. Mrs. Ruth Graham, of the Cytology Laboratory, tells me that in 60 per cent of patients with proved carcinoma of the stomach her technicians can find malignant cells in washings from the stomach if they collect their own samples. If some relatively disinterested person on the ward collects the fasting gastric sample, this figure drops about 20 per cent. The reason is that her technicians spend a great deal of time washing the stomach in and out with saline solution, having the patient change position, and removing the last few drops of the secretions in the stomach when they finally empty it, because that is where the tumor cells are most likely to be. There were 3 false-positive examinations in 13 cases recently; those patients, of course, may later turn out to have cancer, but up to date no cancer has been found in 3 of 13 patients who were believed to have cytologic evidence of cancer. A negative or unsatisfactory smear does not help me a great deal.

When I was studying this protocol I was interested in the question of polyps and reviewed some of the literature. Although it apparently has no bearing at the moment, I might mention it. In 1930 Miller[1] found that 8 of 23 polyps that he studied had carcinoma in them. In 1934 Benedict and Allen[2] found 17 polyps of the stomach in this hospital, 41 per cent of which showed some tendency to become malignant. In 1936 Rigler[3] presented 2 interesting cases in each of which a polyp was removed from the stomach by a local resection; both patients developed cancer of the stomach in the sites of resection forty-eight and eighteen months later. So polyps of the stomach are certainly precursors of cancer. If this patient did not have a polyp, that does not help me, although I suppose a small polyp might have been missed.

Secondly, what is the significance of carcinoma in situ? As I understand it, carcinoma in situ consists of cancer cells limited to the mucosa and does not invade the deep layers of the organ involved. Other carcinomas in situ occur in the skin — Bowen's disease — and in the cervix, where Younge, Hertig and Armstrong[4] found that definite cancer developed in 6 of 135 of their cases. Carcinoma in situ of the stomach was first described as far as I can determine in this hospital by Mallory[5] in 1940. He reported 4 cases in the prepyloric area, in 1 of which carcinoma in situ was related to a polyp and in 1 of which there was extension 1 cm. into the wall of the stomach beyond the actual visible edge of any polypoid tissue.

In summary, the question is, What caused obstruction in the distal end of this patient's stomach? It is true that the obstruction may have been due to an ulcer that formed at the operative site or an ulcer in the duodenum that was not apparently proved; it may also have been due to recurrent redundant mucosa. I think that actually this patient had carcinoma in the stomach in the area of his previously locally excised carcinoma in situ. The history, the symptoms, the weight loss and the x-ray picture are in favor of this. One thing I might add is that this stomach was not very large for a patient who had obstruction from a stenosing duodenal ulcer or scar tissue in that area that gradually occluded the bowel lumen. When cancer occurs in the antrum, the stomach does not have as much chance to grow big as it does with pyloric obstruction from ulcer. I think the patient also had gout, gouty nephritis and arteriosclerotic heart disease.

A PHYSICIAN: How did you explain the hemoglobin?

DR. WHEELOCK: We see 17 gm. of hemoglobin occasionally. I did not think it was high enough to make the diagnosis of any primary blood disease.

A PHYSICIAN: Would you comment on the statement that a patient with a duodenal ulcer does not have cancer?

DR. WHEELOCK: I do not think that is true. I think patients with duodenal ulcers may have cancer of the stomach. Smith and Jordan,[6] a few years ago, wrote a paper in which they cited the exact figures; I think about 30 per cent of patients with malignant ulcer of the stomach had x-ray evidence of previous duodenal ulcer.

DR. EDWARD B. BENEDICT: I should like to raise some questions. When carcinoma in situ is reported and the adequacy of margin is not determined, should not serial sections be done to find out if the margin is adequate? Secondly, with carcinoma in situ when there is any doubt about the margin, should it not always be followed by a subtotal gastrectomy? Thirdly, in this patient it sounds to me as if the follow-up study was inadequate; apparently he was not seen in three years. Perhaps that was the patient's fault. Lastly, when he was seen three years later, apparently no gastroscopy was done. With due respect to the Department of Radiology — and the radiologists would agree — an operative deformity throws them off on re-examination of the stomach by x-ray films. It seems to me that he should have had a gastroscopy.

DR. VICTOR G. BALBONI: This patient was followed quite frequently. We saw him every six months at the longest and sometimes more frequently. He had epigastric distress from the time of the operation. Several x-ray films taken during this period failed to give evidence of cancer. When he came back from Florida this spring, he had about the same epigastric symptoms that he had had over the years since the operation, — perhaps a little more severe, — and in addition he had experienced a few episodes of vomiting. Cancer of the stomach was suspected, and he was hospitalized for study. He was a disturbing case because he looked well, was feeling well, was not anemic and had free hydrochloric acid in the stomach; the cytologic smear was unsatisfactory on two attempts; the radiologists said he was completely obstructed, which he was not because food was going through and he had vomited only a few times before coming in. We did not really know what to do with him but decided, on the basis of the previous lesion, that he should be explored for possible carcinoma of the stomach or stenosis of the lower portion of the stomach secondary to the first operation. The cardiac status made him a poor operative risk.

DR. HANELIN: It is unfortunate that he did not have films directly after the operation; this is frequently the only way we can tell whether change has occurred over and above what has been produced by the surgery. One would suspect if it turns out to have been carcinoma that the lesion was visible in the examination two years before the fourth admission, but without a base line it would be fair to assume that the changes were due to surgery alone.

DR. CASTLEMAN: I think the point about making serial sections to find out whether there is tumor in the resection edge should be discussed. When the piece of tissue is large, it is relatively easy to determine whether or not there is a sufficient margin. When the piece is so small that it is necessary to make serial sections to find out if tumor is at the resected edge, the margin almost certainly is not adequate.

DR. BENEDICT: Then the surgeons were too close in this case.

DR. CASTLEMAN: Yes; they were too close. Your point that when tumor is too close to a resection edge a wider area should be removed at the site of the original resection is also valid. That is the common practice with skin cancers, for instance, in which the scar and the surrounding area is removed whenever tumor is close to the resection edge. Perhaps that should have been done here. Why did the surgeon elect not to go back, Dr. Balboni?

DR. BALBONI: The reason was that this man had a myocardial infarction within six months, had had numerous operations in the past, had only one kidney and, after this operation, manifested bilateral thrombophlebitis and pulmonary emboli with infarction and almost died. We believed that he could not stand another procedure at that time.

CLINICAL DIAGNOSIS

?Carcinoma of stomach.

DR. FRANK C. WHEELOCK'S DIAGNOSES

Carcinoma of stomach.
Gouty nephritis.
Arteriosclerotic heart disease.

ANATOMICAL DIAGNOSIS

Carcinoma in situ of stomach.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The surgeon, who did both operations, said that at the second operation the findings were quite similar to those at the first operation five years before. In the specimen that was removed at the second operation, the mucosa was herniated into the pyloric opening, which was quite large, measuring 7.5 cm. in circumference when it was cut open. We were able to insert a probe around the projecting mucosa before opening the pylorus so that it was not completely obstructed. As Dr. Balboni said, I think food could get through. The mucosa was markedly thickened, pebbly and slightly granular at the antrum.

In sections of the specimen from the first operation five years before the last admission the mucosa was dense and contained an area that proved to be carcinoma in situ. It was limited to the surface epithelium and did not extend down to the submucosa (Fig. 3 and 4). The second specimen showed exactly the same microscopical appearance — the part of the tumor of the antrum that was projecting into the duodenum showed anaplastic carcinoma that was entirely limited to the mucosa except in one spot, where it was beginning to invade;

the rest of the specimen was normal. There was no evidence of involvement of the regional lymph nodes.

This is the first time that we have been able to follow carcinoma in situ of the stomach that we know was present for five years. In this case there was perhaps a little more growth of the lesion, with only a trace of invasion five years later. The chances of cure, I believe, are excellent.

DR. ALLEN G. BRAILEY: Do you think this is an especially benign brand of carcinoma, or is it the usual life history of carcinoma that you happened to catch at a very early stage?

DR. CASTLEMAN: Certainly, this type of carcinoma behaves differently from the usual carcinoma of the stomach.

DR. BRAILEY: Why might not any type of carcinoma begin in this way?

DR. CASTLEMAN: Some carcinomas probably do begin in this fashion, since any carcinoma must start as a change in a single cell or in a group of cells. It is not uncommon to find carcinoma in situ contiguous or close to an obviously invasive carcinoma. We still know too little about cancer, especially its relation to the host.

DR. BRAILEY: Most cancers are not seen until they are advanced.

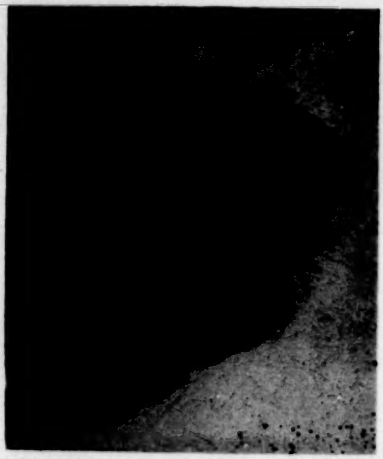

FIGURE 3. *Photomicrograph, Showing Sharp Change from Normal Mucosa at the Top to Dense Carcinoma in Situ Involving the Entire Width of the Mucosa below.*

DR. BALBONI: Would you comment on carcinoma in situ as it occurs in other parts of the body? I have heard that carcinoma in situ of the cervix may remain localized for many years.

DR. CASTLEMAN: That is true. Carcinoma in situ may remain anywhere in the body for long periods. For example, Bowen's disease of the skin may remain ten or twenty years as an in situ lesion and if the patient lives long enough may become invasive. Schiller watched a carcinoma in situ of the cervix with yearly biopsies for seven years; in the seventh year it became invasive.

FIGURE 4. *Higher Magnification, Showing Cellular Details of the Carcinoma in Situ.*

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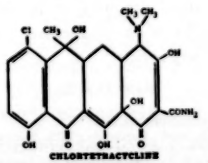
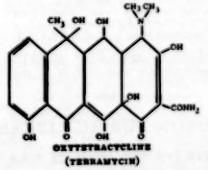
NEW GENERIC NAMES FOR ANTIBIOTICS

ONE of the recent accomplishments in the development of antibiotics that was not only outstanding and fundamental but also a brilliant feat in the field of analytical chemistry was the identification and establishment of the chemical structures of Terramycin and Aureomycin. Interestingly enough, identical results and conclusions were reached almost simultaneously by two groups of chemists working independently and by different methods, one group in the Research Laboratory of Charles Pfizer and Company (with the collaboration, in the final phases, of Professor R. B. Woodward, of the Converse Laboratories of Harvard University) and the other in the Lederle Laboratories. The results confirmed what had long been suspected from the almost identical activities of these two antibiotics and from the almost complete cross-resistance between them — namely, that their basic structure is the same and that they differ in only relatively minor respects.

The final details of the chemical results were described by these two groups of workers within a short time of each other,[1-3] and the announcement that the structure of the two antibiotics had been solved was made simultaneously by workers from both laboratories at the Section of Medicinal Chemistry of the Gordon Conferences sponsored by the American Association for the Advancement of Science in London, New Hampshire, in August, 1952.[4] It was found that the basic structure of both Terramycin and Aureomycin is an entirely unique type not previously encountered; it consists of a cycle of four rings in series with some simple molecules or groups attached to some of the carbon atoms. Moreover, most of these added molecules or groups are identical, both in substance and in position, in the structure of both antibiotics. The only differences in structure are the Cl in Aureomycin, which is absent from Terramycin, and an OH group at another position in Terramycin, which is not present in Aureomycin. The presence of organic chlorine in Aureomycin and its absence from Terramycin was the only difference in chemical structure that was known with certainty before these new revelations. The respective formulas are as follows:





The chemically descriptive name suggested by one of the groups of workers for the basic structure that the two antibiotics have in common was

tetracycline[3]; the chemically descriptive name for Terramycin would, therefore, be oxytetracycline,[3] and it follows that the name for Aureomycin should then be chlorotetracycline or chlortetracycline. The recommendation that these chemically descriptive names should be adopted as the generic designations of these two antibiotics was made editorially in the *Journal of the American Medical Association* last January.[5] The terms "chlortetracycline" and "oxytetracycline" have now been accepted as descriptive of the respective chemical structures by both the *United States Pharmacopoeia* and the Council on Pharmacy and Chemistry of the American Medical Association.[4, 6] The designation oxytetracycline has been in use in all the publications of the Association since last January.

The original designations, Terramycin and Aureomycin, are now retained by the respective manufacturers, Charles Pfizer and Company and the Lederle Laboratories, Division of the American Cyanamid Company, and have become the trade names for the products. In keeping with the policy of the *Journal* and conforming to the style used by the American Medical Association in its journals, only the generic and chemically descriptive names, chlortetracycline and oxytetracycline, will in future be used in the text of articles; the designations Aureomycin and Terramycin will be used only in footnotes, where they will be noted as being the respective trademark equivalents for the manufacturers' products, or in parentheses or quotation marks when the generic name is first mentioned in any article.

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BOSTON PUBLIC LIBRARY

In days that try the souls of men who prize a heritage of freedom, when even the figurative destruction of books and the suppression of knowledge, however distasteful that knowledge may be, become matters of serious discussion, the centennial celebration of the founding of the first free public library to be established in any American city should be an especially significant occasion. This is about to take place in Boston, where the trustees of the Public Library have set aside the months beginning in the fall of 1953 and continuing through the spring of 1954 as such a period of commemoration.

This period is indeed for Boston one when minds are turned toward its great libraries, for the Boston Medical Library celebrated its seventy-fifth anniversary in 1950 and is currently engaged in a campaign to improve its physical facilities and institute a program for greater service to the community. It is also of interest to remember that the Medical Library early in its career became the repository of the medical contents of the Boston Public Library.

The approaching observances of the Public Library's centennial, important as they will be in a cultural sense, have also their practical aspects. Anniversary gifts will be sought, including individual books and collections of books, and funds for the development of expanded library services will be solicited. The celebration will also be the occasion for a campaign for subscriptions to meet the capital needs of the Library, including a necessary enlargement of the central Library building in Copley Square.

Although the Library derives its major support from municipal funds it has never been entirely tax-supported, nor should the citizen of Greater Boston feel that no voluntary support is necessary. The original founding of the Library was made possible by the gifts of the public-spirited citizens, and throughout the century of its existence it has been the recipient of further gifts both of money and of rare books and book collections. So far as present trends are concerned it is of interest that whereas on a national basis public libraries receive an average of 12.2 per cent of their total income from private sources, the Boston Public Library received only 2.3 per cent from independent donors in 1951. This is a trend that must be reversed in the months ahead.

A nine-month period, culminating with the hundredth anniversary of the opening of the

rary's first building on May 2, 1854, has been ected. If this orthodox time schedule is marked normal development, it stands to reason that, n spring comes north again, the Centennial nmission will not have labored in vain.

BIBLIOGRAPHY OF OLIVER WENDELL HOLMES

HE New York University Press on June 26 something of a march on local publishing lities by producing the most up to date and plete bibliography of Oliver Wendell Holmes ecord. This 900-page compendium by Thomas nklin Currier, edited by Eleanor M. Tilton the Bibliographical Society of America, repre- s at this moment certainly the latest if not the word on the Amiable Autocrat, as Miss Tilton er own biography of him dubbed the New Eng- medical profession's favorite author, anatomist wit.

ot only has Dr. Holmes seemed to many of the r local medical and literary inhabitants to be ething in the nature of personal property, but ad intermittent associations with the *Journal's* odical predecessor, the *Boston Medical and ical Journal*, that were like transfusions of al erythrocytes to that aspiring publication. , "The Contagiousness of Puerperal Fever," nes' medical masterpiece, appeared in the short- *New England Quarterly Journal of Medicine Surgery*, which soon after disappeared from , perhaps sunk by the weight of its own title, the *Boston Medical and Surgical Journal* was epository of other of his felicitous essays. us, there appeared on June 1, 1882, "Medical ways and By-ways, A Lecture Delivered before tudents of the Medical Department of Harvard ersity, May 10, 1882," in which he returned e attack on homeopathy, and in short order Farewell Address of Dr. Oliver Wendell Holmes e Medical School of Harvard University, Tues- November 28, 1882," published on December year later, on October 18, 1883, his last paper *Journal* appeared. This was "The New Cen- and the New Building of the Medical School arvard University," an address delivered on October 17. At its close Dr. Holmes' portrait was presented to the School by Dr. Francis Minot.

It is a source of gratification to welcome the present bigger and better bibliography of Dr. Holmes even if published by a foreign university in an alien land. It must be remembered by all borrowers, however, that the amiable autocrat belongs in the Back Bay, although born in distant Cambridge, and must be returned to his owners.

EXECUTIVES' DIGEST

THE editors of the *Journal* are flattered at having been added, at long last, to the mailing list of the four-page *Executives' Digest*. Or perhaps the issue recently received is the initial number of a new abstract journal devoted to the alimentation of published material bearing on administration, organization and possibly execution. The editors, seeing in this gesture a hope of being classed at least among the junior executives, have taken the new publication to their hearts.

Two abstracts caught the editors' collective eye. The first, entitled "Can Executives Be Taught to Think?" and taken from *Fortune*, might be said, in fact, to have caught them between the eyes. In company with "Hundreds of companies" that "are trying out various techniques aimed at improving the mental powers of executives" they, too, feel the subtle sting of the question.

The other item, "Management by Committee," also from *Fortune*, seems still further to complicate the same problem — "shall committees be run as advisory bodies to decision-making individuals, or shall they be run as decision-making groups to which individuals contribute?" One is reminded of the old definition of the ideal committee, attributed by some to Edward Everett Hale and by others to others. The ideal committee is composed of three members, one of whom is in bed with a chronic, disabling disease, and another of whom is spending the year in Europe.

We see it stated in the papers that camphor has been discovered to be an antidote to that terrible poison, strychnine.

Boston M. & S. J., *September 21, 1853*

MASSACHUSETTS MEDICAL SOCIETY

STATED MEETING OF THE COUNCIL

A stated meeting of the Council will be held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston, on Wednesday, October 7, at 10:30 a.m.

Business:

1. Call to order at 10:30 a.m.
2. Presentation of record of meeting held May 19, 1953, as published in Supplement No. 1, July 30, 1953, Vol. 249.
3. Reports of standing and special committees.
4. Such other business as may legally come before this meeting.

ROBERT W. BUCK, M.D.
Secretary

CORRESPONDENCE

GAMMA GLOBULIN AND POLIOMYELITIS

To the Editor: The editorial entitled "Poliomyelitis Prevention and Gamma Globulin — a Reorientation," which appeared in the July 9 issue of the *Journal*, offers "serious criticism on the basis of biostatistics" of the conclusions drawn by Hammon and his associates. These authors based their argument on a 2 x 4 contingency table, columns consisting of treated and control groups (values from three epidemic areas, which were pooled correctly in the absence of a significant x^2 interaction term), and rows giving a classification according to various intervals after inoculation. They performed an x^2 analysis of this table (based on 104 cases) and concluded that gamma globulin gave "highly significant protection against paralytic poliomyelitis."

The editorial criticism states that 500 instead of 104 cases would have been needed to make the result "highly significant" and that "results in these 104 cases cannot be taken as a satisfactory evaluation of such protection . . . It is the variation in incidence [of paralysis in poliomyelitis] that requires at least 500 cases."

This statement can only be understood as implying that the critic uses or requires unusually high significance levels. Indeed, he would require an x^2 of about 100 corresponding to a chance probability $P = 10^{-23}$, whereas contemporary convention attaches high significance to $P \leq 10^{-3}$ and significance to $P \leq 5 \times 10^{-2}$.

As far as the variation in incidence of paralysis is concerned, nothing is known or predicted about the effect of gamma globulin on epidemics with different incidences. There might be an interaction of gamma globulin with incidence such that in severe epidemics gamma globulin would not be demonstrably protective. The proper analysis measuring this interaction would require data from epidemics with different incidences. The effect of variation of incidence on the gamma-globulin effect could not have been assessed by an increase in the number of observations to 500 or any other value.

The significant modification of the severity of the disease obtained with gamma globulin is not inferred from Table 3 and 4 of Paper No. 3, as the editorial assumes, but from a 2 x 2 table following Table 4 of Paper No. 4. Here the chance probability is <0.02. This result the authors have therefore called significant, adopting generally accepted significance levels.

Extension of field trials for the sole purpose of decreasing P values already significant might deprive control patients of the moderate benefits established.

D. KODLIN, M.D.

Pittsburgh, Pennsylvania

NOTICES

ANNOUNCEMENTS

Dr. Arthur N. Kelly announces the opening of an office fo the general practice of medicine at 203 Lindbergh Avenue Needham Heights.

Dr. Anthony Zovickian announces the opening of an office fo the practice of plastic and reconstructive surgery at 270 Com monwealth Avenue, Boston.

EASTERN SECTION OF AMERICAN TRUDEAU SOCIET

The annual meeting of the Eastern Section, American Trudea Society, will be held at the Eastland Hotel, Portland, Main on October 23 and 24. Reservations should be made direct with the hotel.

The program will be on tuberculosis, other chest diseases a cardiac problems. Among the special topics will be virulence tubercle bacilli from isoniazid-treated patients, late follow-u study of patients treated with chemotherapy and early, comple mobilization, recent advances in the treatment of severe pulm nary emphysema, a comparative review of thoracoplasty a resection in the treatment of pulmonary tuberculosis, surgic treatment of mitral insufficiency, acute respiratory acidos pulmonary tumors and revascularization of the myocardium the treatment of coronary insufficiency.

All interested physicians are cordially invited to attend.

NEW YORK SOCIETY FOR CIRCULATORY DISEAS

The ninth regular meeting of the New York Society f Circulatory Diseases of the American College of Cardiology w be held in room 440, New York Academy of Medicine buildi 2 East 103 Street, New York City, on Tuesday, October 13, 8:30 p.m. The program will comprise a symposium on rehabili tion of the cardiac patient. The speakers will include D Samuel Kahn, Herman J. Bennett, Abraham Jezer and Ir Klein. Further information may be obtained from the secreta Dr. Gabriel F. Greco, 114-08 Linden Boulevard, Ozone Park New York.

AMERICAN COLLEGE OF CARDIOLOGY

The fall meeting of the American College of Cardiology will held at the Hotel Statler, Cleveland, Ohio, on November 6 an The topic of the meeting will be congenital heart disease. Furt information may be obtained from the Secretary, Dr. Ph Reichert, 480 Park Avenue, New York 22, New York.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 23. Middlesex South District Medical Society. Page issue of August 6.
SEPTEMBER 23. American Medical Writers' Association. Page issue of August 27.
SEPTEMBER 23. Massachusetts Academy of General Practice. Clinical Assembly. Page 470, issue of September 10.
SEPTEMBER 23-25. Mississippi Valley Medical Society. Page 386, i of August 27.
SEPTEMBER 24-OCTOBER 1. Fourth Congress of Pan American Med Women's Alliance. Page 124, issue of July 16.
SEPTEMBER 30. New England Pediatric Society.
SEPTEMBER 30. Essex North District Medical Society. Page 470, i of September 10.
OCTOBER 2. Phi Delta Annual Lecture. Page 470, issue of Septembe
OCTOBER 4-9. American Academy of Pediatrics. Page 1126, issu June 25.
OCTOBER 5-DECEMBER 7. Postgraduate Seminar in Neurology and P chiatry. Page 428, issue of September 3.
OCTOBER 5-DECEMBER 21. Hartford Medical Society Program. P 260, issue of August 6.
OCTOBER 7-DECEMBER 2. Course in child psychiatry (pediatric ne psychiatry). Page 428, issue of September 3.
OCTOBER 8. New York Diabetic Association. Page 470, issu September 10.
OCTOBER 12-14. National Gastroenterological Association. Page issue of August 6.
OCTOBER 12-14. Medical and Dental Military Symposium. Page issue of September 10.
OCTOBER 12-17. Seventh International Congress of Pediatrics. P 170, issue of July 23.
OCTOBER 13. New York Society for Circulatory Diseases. Notice ab

(*Notices concluded on page xxiii*)